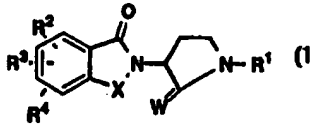
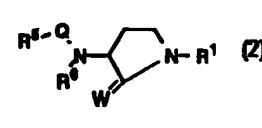


PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: C07D 207/12, 209/12, 209/34, 217/24, 401/04, A61K 31/405, 31/47, 31/395	A1	(11) International Publication Number: WO 97/43257 (43) International Publication Date: 20 November 1997 (20.11.97)
(21) International Application Number: PCT/US97/07603 (22) International Filing Date: 6 May 1997 (06.05.97) (30) Priority Data: 60/017,253 10 May 1996 (10.05.96) US (71) Applicant: BRISTOL-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Princeton, NJ 08543-4000 (US). (72) Inventors: DICKSON, John, K., Jr.; 14 Shelter Rock Road, Eastampton, NJ 08060 (US). ROBL, Jeffrey, A.; 7 Tulip Drive, Newtown, PA 18940 (US). BILLER, Scott, A.; 31 Second Street, Hopewell, NJ 08525 (US). (74) Agents: RODNEY, Burton et al.; Bristol-Myers Squibb Com- pany, P.O. Box 4000, Princeton, NJ 08543-4000 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: INHIBITORS OF MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN AND METHOD		
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>(1)</p> </div> <div style="text-align: center;">  <p>(2)</p> </div> </div>		
(57) Abstract Compounds are provided which inhibit microsomal triglyceride transfer protein and thus are useful for lowering serum lipids and treating atherosclerosis and related diseases. The compounds have structure (1) or (2) wherein R ¹ to R ⁶ , Q, W and X are as defined herein.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

**INHIBITORS OF MICROSOMAL TRIGLYCERIDE TRANSFER
PROTEIN AND METHOD**

Field of the Invention

5 This invention relates to novel compounds
which inhibit microsomal triglyceride transfer
protein, and to methods for decreasing serum
lipids and treating atherosclerosis employing such
10 compounds.

Background of the Invention

 The microsomal triglyceride transfer
protein (MTP) catalyzes the transport of
triglyceride (TG), cholesteryl ester (CE), and
15 phosphatidylcholine (PC) between small unilamellar
vesicles (SUV). Wetterau & Zilversmit, Chem.
Phys. Lipids 38, 205-22 (1985). When transfer
rates are expressed as the percent of the donor
lipid transferred per time, MTP expresses a
20 distinct preference for neutral lipid transport
(TG and CE), relative to phospholipid transport.
The protein from bovine liver has been isolated
and characterized. Wetterau & Zilversmit, Chem.
Phys. Lipids 38, 205-22 (1985). Polyacrylamide
25 gel electrophoresis (PAGE) analysis of the
purified protein suggests that the transfer
protein is a complex of two subunits of apparent
molecular weights 58,000 and 88,000, since a
single band was present when purified MTP was
30 electro-phoresed under nondenaturing condition,
while two bands of apparent molecular weights
58,000 and 88,000 were identified when
electrophoresis was performed in the presence of
sodium dodecyl sulfate (SDS). These two
35 polypeptides are hereinafter referred to as 58 kDa
and 88 kDa, respectively, or the 58 kDa and the 88
kDa component of MTP, respectively, or the low

molecular weight subunit and the high molecular weight subunit of MTP, respectively.

Characterization of the 58,000 molecular weight component of bovine MTP indicates that it is the previously characterized multifunctional protein, protein disulfide isomerase (PDI). Wetterau *et al.*, *J. Biol. Chem.* 265, 9800-7 (1990). The presence of PDI in the transfer protein is supported by evidence showing that (1) the amino terminal 25 amino acids of the bovine 58,000 kDa component of MTP is identical to that of bovine PDI, and (2) disulfide isomerase activity was expressed by bovine MTP following the dissociation of the 58 kDa - 88 kDa protein complex. In addition, antibodies raised against bovine PDI, a protein which by itself has no TG transfer activity, were able to immunoprecipitate bovine TG transfer activity from a solution containing purified bovine MTP.

PDI normally plays a role in the folding and assembly of newly synthesized disulfide bonded proteins within the lumen of the endoplasmic reticulum. Bulleid & Freedman, *Nature* 335, 649-51 (1988). It catalyzes the proper pairing of cysteine residues into disulfide bonds, thus catalyzing the proper folding of disulfide bonded proteins. In addition, PDI has been reported to be identical to the beta subunit of human prolyl 4-hydroxylase. Koivu *et al.*, *J. Biol. Chem.* 262, 6447-9 (1987). The role of PDI in the bovine transfer protein is not clear. It does appear to be an essential component of the transfer protein as dissociation of PDI from the 88 kDa component of bovine MTP by either low concentrations of a denaturant (guanidine HCl), a chaotropic agent (sodium perchlorate), or a nondenaturing detergent (octyl glucoside) results in a loss of transfer

activity. Wetterau et al., Biochemistry **30**, 9728-35 (1991). Isolated bovine PDI has no apparent lipid transfer activity, suggesting that either the 88 kDa polypeptide is the transfer protein or that it confers transfer activity to the protein complex.

The tissue and subcellular distribution of MTP activity in rats has been investigated. Wetterau & Zilversmit, Biochem. Biophys. Acta **875**, 610-7 (1986). Lipid transfer activity was found in liver and intestine. Little or no transfer activity was found in plasma, brain, heart, or kidney. Within the liver, MTP was a soluble protein located within the lumen of the microsomal fraction. Approximately equal concentrations were found in the smooth and rough microsomes.

Abetalipoproteinemia is an autosomal recessive disease characterized by a virtual absence of plasma lipoproteins which contain apolipoprotein B (apoB). Kane & Havel in The Metabolic Basis of Inherited Disease, Sixth Edition, 1139-64 (1989). Plasma TG levels may be as low as a few mg/dL, and they fail to rise after fat ingestion. Plasma cholesterol levels are often only 20-45 mg/dL. These abnormalities are the result of a genetic defect in the assembly and/or secretion of very low density lipoproteins (VLDL) in the liver and chylomicrons in the intestine. The molecular basis for this defect has not been previously determined. In subjects examined, triglyceride, phospholipid, and cholesterol synthesis appear normal. At autopsy, subjects are free of atherosclerosis. Schaefer et al., Clin. Chem. **34**, B9-12 (1988). A link between the apoB gene and abetalipoproteinemia has been excluded in several families. Talmud et al., J.

Clin. Invest. 82, 1803-6 (1988) and Huang et al.,
Am. J. Hum. Genet. 46, 1141-8 (1990).

Subjects with abetalipoproteinemia are afflicted with numerous maladies. Kane & Havel,
5 supra. Subjects have fat malabsorption and TG accumulation in their enterocytes and hepatocytes. Due to the absence of TG-rich plasma lipoproteins, there is a defect in the transport of fat-soluble vitamins such as vitamin E. This results in
10 acanthocytosis of erythrocytes, spinocerebellar ataxia with degeneration of the fasciculus cuneatus and gracilis, peripheral neuropathy, degenerative pigmentary retinopathy, and ceroid myopathy. Treatment of abetalipoproteinemic
15 subjects includes dietary restriction of fat intake and dietary supplementation with vitamins A, E and K.

In vitro, MTP catalyzes the transport of lipid molecules between phospholipid membranes.
20 Presumably, it plays a similar role in vivo, and thus plays some role in lipid metabolism. The subcellular (lumen of the microsomal fraction) and tissue distribution (liver and intestine) of MTP have led to speculation that it plays a role in
25 the assembly of plasma lipoproteins, as these are the sites of plasma lipoprotein assembly. Wetterau & Zilversmit, Biochem. Biophys. Acta 875, 610-7 (1986). The ability of MTP to catalyze the transport of TG between membranes is consistent
30 with this hypothesis, and suggests that MTP may catalyze the transport of TG from its site of synthesis in the endoplasmic reticulum (ER) membrane to nascent lipoprotein particles within the lumen of the ER.

35 Olofsson and colleagues have studied lipoprotein assembly in HepG2 cells. Bostrom et al., J. Biol. Chem. 263, 4434-42 (1988). Their

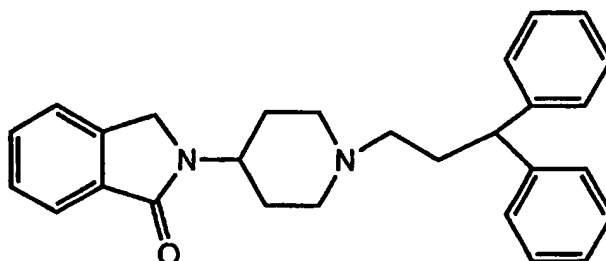
results suggest small precursor lipoproteins become larger with time. This would be consistent with the addition or transfer of lipid molecules to nascent lipoproteins as they are assembled.

- 5 MTP may play a role in this process. In support of this hypothesis, Howell and Palade, J. Cell Biol. 92, 833-45 (1982), isolated nascent lipoproteins from the hepatic Golgi fraction of rat liver. There was a spectrum of sizes of
- 10 particles present with varying lipid and protein compositions. Particles of high density lipoprotein (HDL) density, yet containing apoB, were found. Higgins and Hutson, J. Lipid Res. 25, 1295-1305 (1984), reported lipoproteins isolated
- 15 from Golgi were consistently larger than those from the endoplasmic reticulum, again suggesting the assembly of lipoproteins is a progressive event.

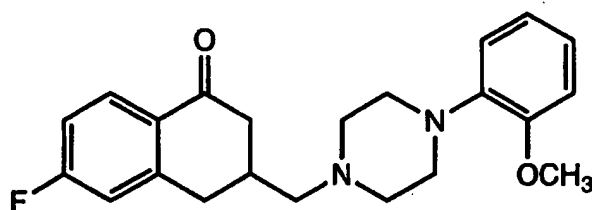
- Recent reports (Science, Vol. 258, page
- 20 999, 1992; D. Sharp et. al., Nature, Vol. 365, page 65, 1993) demonstrate that the defect causing abetalipoproteinemia is in the MTP gene, and as a result, the MTP protein. Individuals with abetalipoproteinemia have no MTP activity, as a
- 25 result of mutations in the MTP gene, some of which have been characterized. These results indicate that MTP is required for the synthesis of apoB containing lipoproteins, such as VLDL, the precursor to LDL. It therefore follows that
- 30 inhibitors of MTP would inhibit the synthesis of VLDL and LDL, thereby lowering VLDL levels, LDL levels, cholesterol levels, and triglyceride levels in animals and man.

- Canadian Patent Application No. 2,091,102
- 35 published March 2, 1994 (corresponding to U.S. application Serial No. 117,362, filed September 3, 1993 (file DC21b)) reports MTP inhibitors which

- also block the production of apoB containing lipoproteins in a human hepatic cell line (HepG2 cells). This provides further support for the proposal that an MTP inhibitor would lower apoB
- 5 containing lipoprotein and lipid levels in vivo. This Canadian patent application discloses a method for identifying the MTP inhibitors



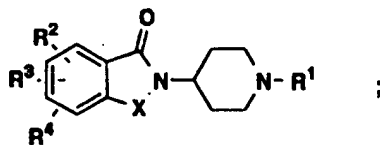
- 10 which has the name 2-[1-(3,3-diphenylpropyl)-4-piperidiny]-2,3-dihydro-3-oxo-1H-indole hydrochloride and



- 15 which has the name 1-[3-(6-fluoro-1-tetralanyl)methyl]-4-O-methoxyphenyl piperazine

EP 0643057A1 published March 15, 1995, discloses MTP inhibitors of the structure

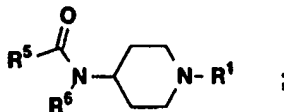
I



20

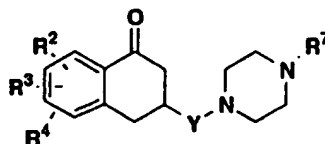
or

II



or

III



where X is: CHR^8 , $\begin{array}{c} -\text{CH}-\text{CH}- \\ | \quad | \\ \text{R}^9 \quad \text{R}^{10} \end{array}$ or $\begin{array}{c} -\text{C}=\text{C}- \\ | \quad | \\ \text{R}^9 \quad \text{R}^{10} \end{array}$;

5

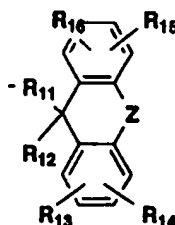
R^8 , R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

10 Y is $-(\text{CH}_2)_m-$ or $\begin{array}{c} -\text{C}- \\ || \\ \text{O} \end{array}$

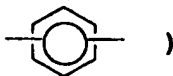
where m is 2 or 3;

R^1 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl (wherein alkyl has at least 2 carbons), diarylalkyl, arylalkenyl, diaryl-
 15 alkenyl, arylalkynyl, diarylalkynyl, diarylalkyl-aryl, heteroarylalkyl (wherein alkyl has at least 2 carbons), cycloalkyl, or cycloalkylalkyl (wherein alkyl has at least 2 carbons); all of the
 20 aforementioned R^1 groups being optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cyclo-
 25 alkylalkyl, heteroaryl, fluorenyl, heteroaryl-alkyl, hydroxy or oxo; or

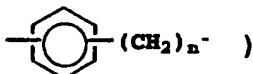
R^1 is a group of the structure



R¹¹ is a bond, alkylene, alkenylene or alkynylene of up to 6 carbon atoms, arylene (for example



5 or mixed arylene-alkylene (for example



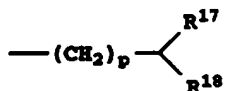
where n is 1 to 6;

R¹² is hydrogen, alkyl, alkenyl, aryl, heteroaryl, haloalkyl, arylalkyl, arylalkenyl, 10 cycloalkyl, aryloxy, alkoxy, arylalkoxy, heteroarylalkyl or cycloalkylalkyl;

Z is a bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene of from 1 to 5 carbon atoms;

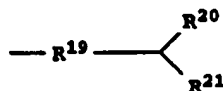
15 R¹³, R¹⁴, R¹⁵, and R¹⁶ are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, 20 carboxy, aminocarbonyl, alkylcarbonyloxy, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

or R¹ is



25 wherein p is 1 to 8 and R¹⁷ and R¹⁸ are each independently H, alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl, at least one of R¹⁷ and R¹⁸ being other than H;

30 or R¹ is



wherein R¹⁹ is aryl or heteroaryl;

R²⁰ is aryl or heteroaryl;

R²¹ is H, alkyl, aryl, alkylaryl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

5 R², R³, R⁴ are independently hydrogen, halo, alkyl, haloalkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

10 R⁵ is alkyl of at least 2 carbons, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, all of the R⁵ and R⁶ substituents being optionally substituted through available carbon atoms with 1, 2, or 3 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, 15 cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkynyl, aryloxy, aryloxyalkyl, aryl-alkoxy, arylazo, heteroaryloxy, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, 20 hydroxy, nitro, cyano, amino, substituted amino (wherein the amino includes 1 or 2 substituents which are alkyl, or aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylamino-carbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylamino-carbonyl, alkylcarbonyloxy, arylcarbonyloxy, 25 alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino; with the proviso that when R⁵ is CH₃, R⁶ is not H; and where R⁵ is ...

phenyl, the phenyl preferably includes an ortho hydrophobic substituent such as alkyl, haloalkyl, aryl, aryloxy or arylalkyl;

5 R^6 is hydrogen or C₁-C₄ alkyl or C₁-C₄ alkenyl;

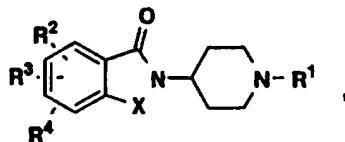
R^7 is alkyl, aryl or arylalkyl wherein alkyl or the alkyl portion is optionally substituted with oxo; and

10 including pharmaceutically acceptable salts and anions thereof.

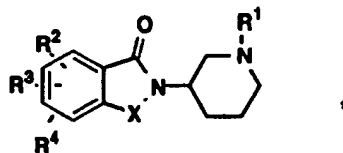
In the formula I compounds, where X is CH₂ and R^2 , R^3 and R^4 are each H, R^1 will be other than 3,3-diphenylpropyl.

15 In the formula III compounds, where one of R^2 , R^3 and R^4 is 6-fluoro, and the others are H, R^7 will be other than 4-O-methoxyphenyl.

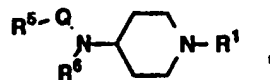
U.S. Application Serial No. 472,067, filed June 6, 1995 (file DC21e) discloses compounds of the structure



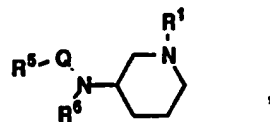
or



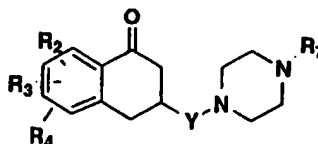
or



or



or



where Q is $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$ or $-\overset{\text{O}}{\underset{\text{O}}{\text{S}}}-$;

5

X is: CHR^8 , $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$, $-\underset{\text{R}^9}{\text{CH}}-\underset{\text{R}^{10}}{\text{CH}}-$ or $-\underset{\text{R}^9}{\text{C}}=\underset{\text{R}^{10}}{\text{C}}-$;

R^8 , R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

10

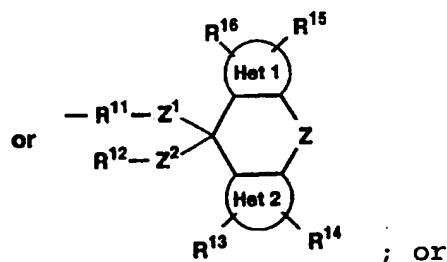
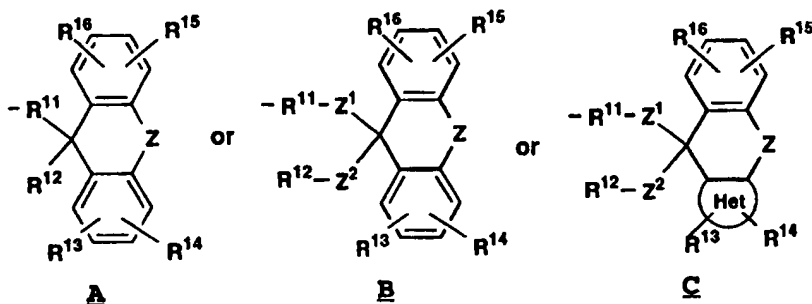
Y is $-(\text{CH}_2)_m-$ or $-\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-$

wherein m is 2 or 3;

R^1 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl wherein alkyl has at least 2 carbons, diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl wherein alkyl has at least 2 carbons, cycloalkyl, or cycloalkylalkyl wherein alkyl has at least 2 carbons, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo;

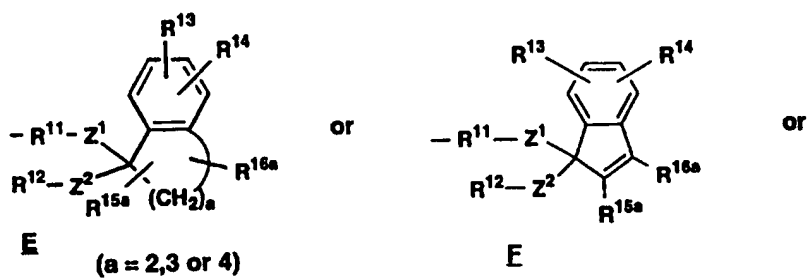
25

or R^1 is a fluorenyl-type group of the structure

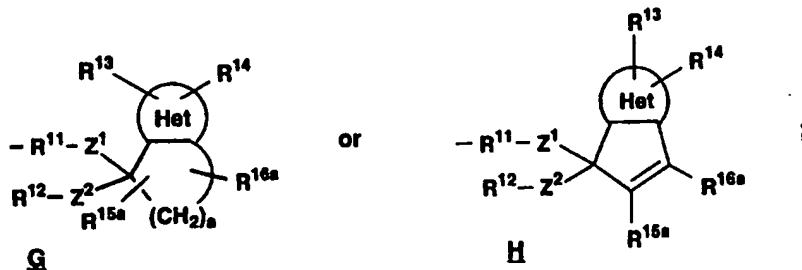


5

R^1 is an indenyl-type group of the structure

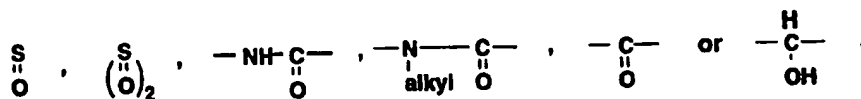


10



15

Z^1 and Z^2 are the same or different and are independently a bond, O, S,



with the proviso that with respect to B, at least one of Z^1 and Z^2 will be other than a bond; R^{11} is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms; arylene or mixed arylene-alkylene; R^{12} is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl, with the provisos that

(1) when R^{12} is H, aryloxy, alkoxy or arylalkoxy, then Z^2 is

$$\begin{array}{c} \text{---NH---C---} \\ \parallel \\ \text{O} \end{array}, \begin{array}{c} \text{---N---C---} \\ | \quad \parallel \\ \text{alkyl} \quad \text{O} \end{array}, \begin{array}{c} \text{---C---} \\ \parallel \\ \text{O} \end{array}$$

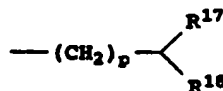
or a bond and

(2) when Z^2 is a bond, R^{12} cannot be heteroaryl or heteroarylalkyl;

Z is bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene from 1 to 5 carbon atoms; R^{13} , R^{14} , R^{15} , and R^{16} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cyclo-heteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl or aryloxy;

R^{15a} and R^{16a} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cyclo-heteroalkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

or R^1 is a group of the structure

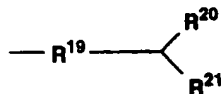


wherein p is 1 to 8 and R^{17} and R^{18} are each independently H, alkyl, alkenyl, aryl, arylalkyl,

heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl at least one of R¹⁷ and R¹⁸ being other than H;

or R¹ is a group of the structure

5



wherein R¹⁹ is aryl or heteroaryl;

R²⁰ is aryl or heteroaryl;

R²¹ is H, alkyl, aryl, alkylaryl,

10 arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

R², R³, R⁴ are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

R⁵ is independently alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl,

25 heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all optionally substituted through available

carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy,

30 haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl,

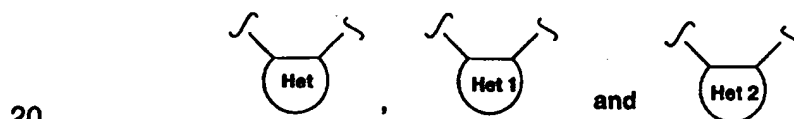
arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxy,

35 heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino,

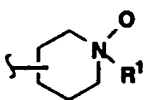
thiol, alkylthio, arylthio, heteroarylthio,
 arylthioalkyl, alkylcarbonyl, arylcarbonyl,
 arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl,
 alkynylaminocarbonyl, alkylaminocarbonyl, alkenyl-
 5 aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy,
 alkylcarbonylamino, arylcarbonylamino, arylsul-
 finyl, arylsulfinylalkyl, arylsulfonyl, alkylsul-
 fonyl, arylsulfonylamino, heteroarylcarbonylamino,
 heteroarylsulfinyl, heteroarylthio, heteroaryl-
 10 sulfonyl, alkylsulfinyl;

R^6 is hydrogen or C₁-C₄ alkyl or C₁-C₄
 alkenyl; all optionally substituted with 1, 2, 3
 or 4 groups which may independently be any of the
 substituents listed in the definition of R^5 set
 15 out above;

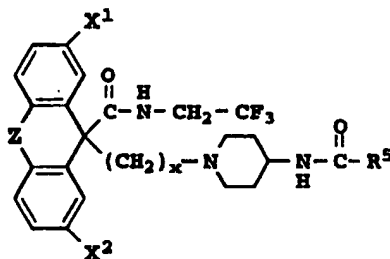
R^7 is alkyl, aryl or arylalkyl wherein
 alkyl by itself or as part of arylalkyl is
 optionally substituted with oxo $\left(\begin{smallmatrix} \text{O} \\ || \end{smallmatrix} \right)$;



are the same or different and are independently
 selected from heteroaryl containing 5- or 6-ring
 members; and

N-oxides  thereof; and
 25 pharmaceutically acceptable salts thereof;
 with the provisos that where in the first
 formula X is CH₂, and R², R³ and R⁴ are each H,
 then R¹ will be other than 3,3-diphenylpropyl, and
 in the fifth formula, where one of R², R³ and R⁴
 30 is 6-fluoro, and the others are H, R⁷ will be
 other than 4-(2-methoxyphenyl).

U.S. application Serial No. 548,811 filed January 11, 1996 (file DC21h), discloses compounds having the structure

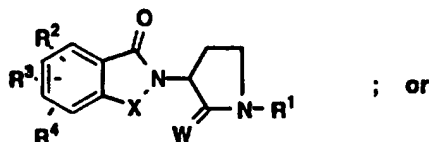


- 5 including the piperidine N-oxide thereof or a pharmaceutically acceptable salt thereof, wherein Z is a bond, O or S;
 10 X^1 and X^2 are independently selected from H or halo;
 x is an integer from 2 to 6;
 R^5 is heteroaryl, aryl, heterocycloalkyl or cycloalkyl, each R^5 group being optionally substituted with 1, 2, 3 or 4 substituents which
 15 may be the same or different.

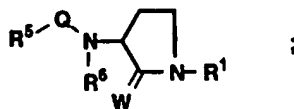
Summary of the Invention

- In accordance with the present invention, novel compounds are provided which are inhibitors
 20 of MTP and have the structure

I



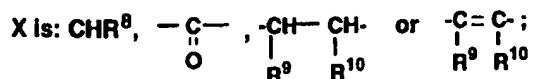
II



25

where Q is $\text{—}\overset{\text{O}}{\parallel}\text{C—}$ or $\text{—}\overset{\text{O}}{\parallel}\text{S—}$;

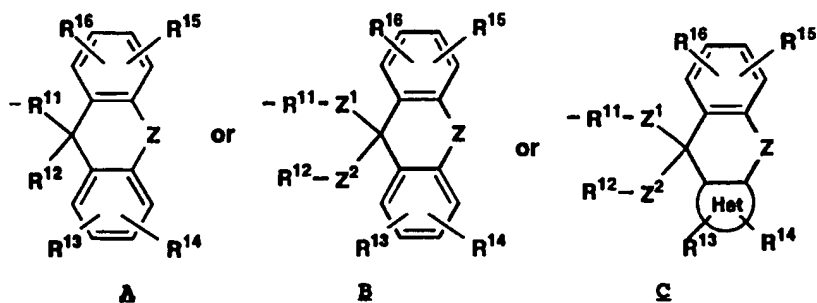
W is H, H or O;

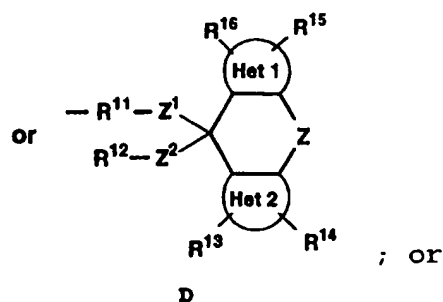


- R^8 , R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;
 R^1 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons), diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons), cycloalkyl, or cycloalkylalkyl (wherein alkyl preferably has at least 2 carbons, more preferably at least 3 carbons); all of the
 aforementioned R^1 groups being optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl, heteroarylalkyl, hydroxy or oxo; or

R^1 is a fluorenyl-type group of the structure

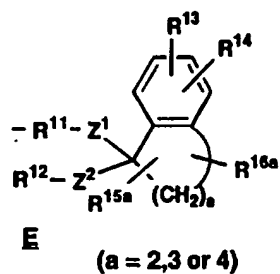
25



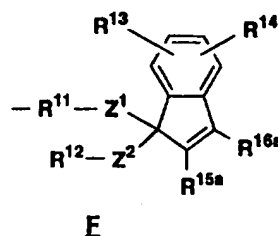


R¹ is an indenyl-type group of the structure

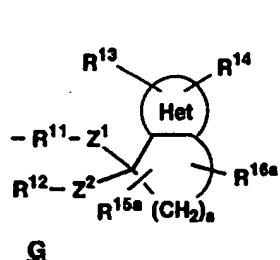
5



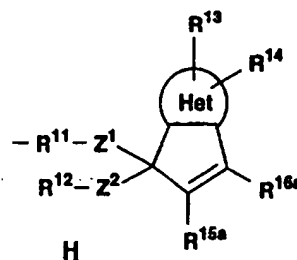
or



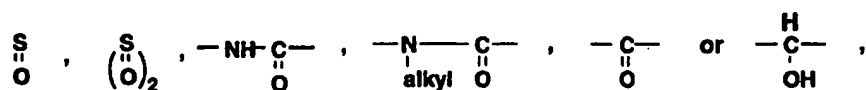
or



or

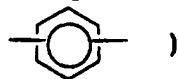


10 Z¹ and Z² are the same or different and are independently a bond, O, S,

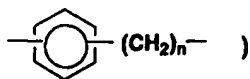


with the proviso that with respect to B, at least one of Z¹ and Z² will be other than a bond;

15 R¹¹ is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms, arylene (for example

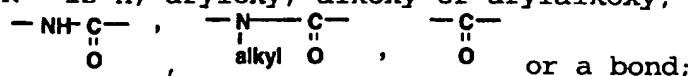


or mixed arylene-alkylene (for example



where n is 1 to 6;

R^{12} is hydrogen, alkyl, alkenyl, aryl, halo-alkyl, trihaloalkyl, trihaloalkylalkyl, hetero-
 5 aryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl; with the provisos that (1) when R^{12} is H, aryloxy, alkoxy or arylalkoxy, then Z^2 is



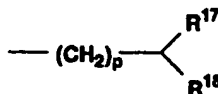
10 and (2) when Z^2 is a bond, R^{12} cannot be heteroaryl or heteroarylalkyl;

Z is a bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene of from 1 to 5 carbon atoms;

15 R^{13} , R^{14} , R^{15} , and R^{16} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio,
 20 aminocarbonyl, alkylcarbonyloxy, arylcarbonyl-amino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

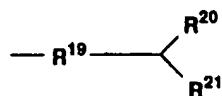
R^{15a} and R^{16a} are independently any of the R^{15} or R^{16} groups except hydroxy, nitro, amino or
 25 thio;

or R^1 is



wherein p is 1 to 8 and R^{17} and R^{18} are each independently H, alkyl, alkenyl, aryl, arylalkyl,
 30 heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl, at least one of R^{17} and R^{18} being other than H;

or R^1 is



wherein R¹⁹ is aryl or heteroaryl;

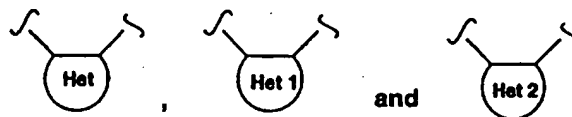
R²⁰ is aryl or heteroaryl;

R²¹ is H, alkyl, aryl, alkylaryl, arylalkyl,
 5 aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl,
 heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or
 cycloalkylalkoxy;

R², R³, R⁴ are independently hydrogen, halo,
 alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl,
 10 alkylmercapto, arylmercapto, cycloalkyl,
 cycloalkylalkyl, heteroaryl, heteroarylalkyl,
 hydroxy or haloalkyl;

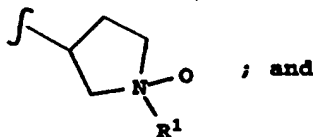
R⁵ is alkyl, alkenyl, alkynyl, aryl,
 alkoxy, aryloxy, arylalkoxy, heteroaryl, aryl-
 15 alkyl, heteroarylalkyl, cycloalkyl, cyclohetero-
 alkyl, heteroaryloxy, cycloalkylalkyl, polycyclo-
 alkyl, polycycloalkylalkyl, cycloalkenyl, cyclo-
 alkenylalkyl, polycycloalkenyl, polycycloalkenyl-
 alkyl, heteroarylcarbonyl, amino, alkylamino,
 20 arylamino, heteroarylamino, cycloalkyloxy, cyclo-
 alkylamino, all of the R⁵ substituents and R⁶
 substituents (set out hereinafter) being
 optionally substituted through available carbon
 atoms with 1, 2, 3 or 4 groups selected from
 25 hydrogen, halo, alkyl, haloalkyl, alkoxy,
 haloalkoxy, alkenyl, alkynyl, cycloalkyl,
 cycloalkylalkyl, cycloheteroalkyl, cyclohetero-
 alkylalkyl, aryl, heteroaryl, arylalkyl,
 arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy,
 30 aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxy,
 heteroarylalkyl, heteroarylalkenyl, heteroaryloxy,
 hydroxy, nitro, cyano, amino, substituted amino
 (wherein the amino includes 1 or 2 substituents
 which are alkyl, aryl or heteroaryl, or any of the
 35 other aryl compounds mentioned in the
 definitions), thiol, alkylthio, arylthio,

- heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylamino-carbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, 5 arylcarbonyloxy, alkylcarbonylamino, arylcarbonyl-amino, arylsulfinyl, arylsulfinylalkyl, aryl-sulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, or 10 alkylsulfinyl. Where R^5 is phenyl, aryl, heteroaryl or cycloalkyl; this group preferably includes an ortho hydrophobic substituent such as alkyl, haloalkyl (with up to 5 halo groups), alkoxy, haloalkoxy (with up to 5 halo groups), 15 aryl, aryloxy or arylalkyl;
 R^6 is hydrogen or C_1 - C_4 alkyl or C_1 - C_4 alkenyl;



- 20 are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and

including N-oxides of the formulae I and II compounds, that is



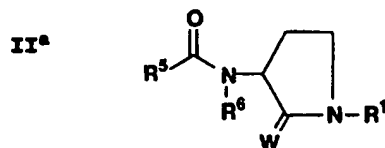
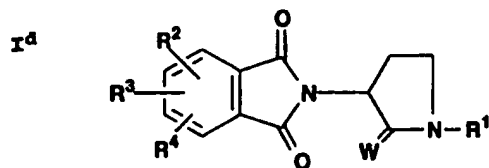
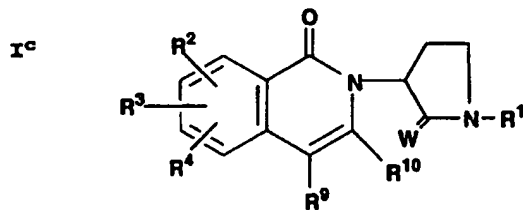
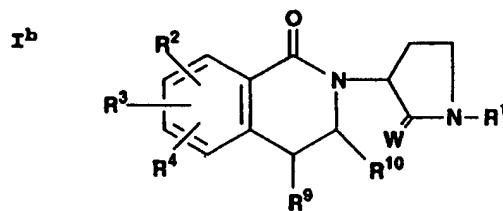
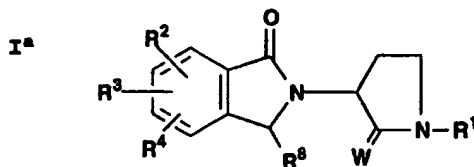
25

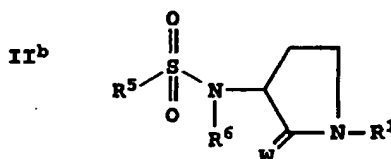
including pharmaceutically acceptable salts thereof such as alkali metal salts such as lithium sodium or potassium, alkaline earth metal salts such as calcium or magnesium, as well as zinc or 30 aluminum and other cations such as ammonium, choline, diethanolamine, ethylenediamine, t-butylamine, t-octylamine, dehydroabietylamine, as well as pharmaceutically acceptable anions such as

chloride, bromide, iodide, tartrate, acetate, methanesulfonate, maleate, succinate, glutarate, and salts of naturally occurring amino acids such as arginine, lysine, alanine and the like, and
 5 prodrug esters thereof.

In the formula I compounds, where X is CH₂ and R², R³ and R⁴ are each H, R¹ will preferably be other than 3,3-diphenylpropyl.

Thus, the compounds of formulae I and II of
 10 the invention encompass compounds of the structure





It will be understood that the pyrrolidinyl ring shown in the above formulas depicting compounds of the invention as well as in starting materials and intermediates shown in the Reaction Schemes to follow can be in racemic form or are R- or S-enantiomers.

In addition, in accordance with the present invention, a method for preventing, inhibiting or treating atherosclerosis, pancreatitis or obesity is provided, wherein a compound of formula I or II as defined hereinbefore is administered in an amount which decreases the activity of microsomal triglyceride transfer protein.

Furthermore, in accordance with the present invention, a method is provided for lowering serum lipid levels, cholesterol and/or triglycerides, or inhibiting and/or treating hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia, wherein a compound of formula I or II is administered in an amount which decreases the activity of microsomal triglyceride transfer protein.

Detailed Description of the Invention

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

The term "MTP" refers to a polypeptide or protein complex that (1) if obtained from an organism (e. g., cows, humans, etc.), can be isolated from the microsomal fraction of homogenized tissue; and (2) stimulates the transport of triglycerides, cholesterol esters, or

phospholipids from synthetic phospholipid vesicles, membranes or lipoproteins to synthetic vesicles, membranes, or lipoproteins and which is distinct from the cholesterol ester transfer protein [Drayna et al., Nature 327, 632-634 (1987)] which may have similar catalytic properties. However, the MTP molecules of the present invention do not necessarily need to be catalytically active. For example, catalytically inactive MTP or fragments thereof may be useful in raising antibodies to the protein.

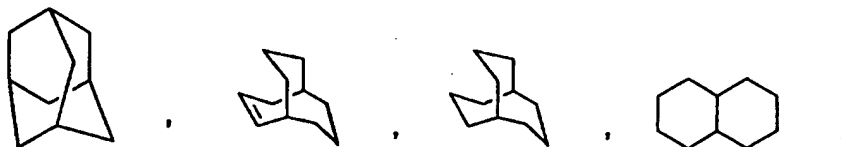
The phrase "stabilizing" atherosclerosis as used in the present application refers to slowing down the development of and/or inhibiting the formation of new atherosclerotic lesions.

The phrase "causing the regression of" atherosclerosis as used in the present application refers to reducing and/or eliminating atherosclerotic lesions.

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 40 carbons, preferably 1 to 20 carbons, more preferably 1 to 12 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents such as halo, for example F, Br, Cl or I or CF₃, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, hydroxy, acyl, heteroaryl, heteroaryloxy, heteroarylalkyl, heteroarylalkoxy, aryloxyalkyl,

aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio, as well as any of the other substituents as defined for R⁵ and R⁶.

- 5 Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and
10 tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 4 to 12 carbons, forming the ring and which may be fused to 1 or 2 aromatic rings as described for aryl,
15 which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,



- 20 any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol
25 and/or alkylthio, as well as any of the other substituents as defined for R⁵ or R⁶.

- The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 5 to 20 carbons,
30 preferably 6 to 12 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, and cycloheptadienyl, which may be optionally substituted as
35 defined for cycloalkyl.

The term "polycycloalkyl" as employed herein alone or as part of another group refers to a bridged multicyclic group containing 5 to 20 carbons and containing 0 to 3 bridges, preferably 6 to 12 carbons and 1 or 2 bridges. Exemplary polycycloalkyl groups include [3.3.0]-bicyclooctanyl, adamantanyl, [2.2.1]-bicycloheptanyl, [2.2.2]-bicyclooctanyl and the like and may be optionally substituted as defined for cycloalkyl.

10 The term "polycycloalkenyl" as employed herein alone or as part of another group refers to a bridged multicyclic group containing 5 to 20 carbons and containing 0 to 3 bridges and containing 1 or 2 double bonds, preferably 6 to 12 carbons and 1 or 2 bridges. Exemplary polycycloalkyl groups include [3.3.0]-bicyclooctenyl, [2.2.1]-bicycloheptenyl, [2.2.2]-bicyclooctenyl and the like and may be optionally substituted as defined for cycloalkyl.

20 The term "aryl" or "Ar" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl) and may optionally include one to three additional rings fused to Ar (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings) and may be optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkyl-alkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxy-alkyl, arylalkoxy, arylthio, arylazo, hetero-arylalkyl, heteroarylalkenyl, heteroarylhetero-aryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or

2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonamino-carbonyl, or any of the substituents as defined for the R⁵ or R⁶ groups set out above.

The term "aralkyl", "aryl-alkyl" or "aryllower alkyl" as used herein alone or as part of another group refers to alkyl groups as discussed above having an aryl substituent, such as benzyl or phenethyl, or naphthylpropyl, or an aryl as defined above.

The term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

The term "amino" as employed herein alone or as part of another group may optionally be substituted with one or two substituents such as alkyl and/or aryl.

The term "lower alkylthio", "alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

The term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

The term "acyl" as employed herein by itself or part of another group as defined herein, refers to an organic radical linked to a carbonyl



group, examples of acyl groups include
5 alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl and the like.

The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

10 Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 3 to 12 carbons, and more preferably 1
15 to 8 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-
20 nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cyclo-
25 alkyl, amino, hydroxy, heteroaryl, cycloheteroalkyl, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol and/or alkylthio, as well as any of the other substituents as defined for R⁵ or R⁶.

30 Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2
35 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butylnyl, 2-butylnyl, 4-pentylnyl, 3-

pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonyl, 4-decynyl, 3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol, and/or alkylthio, as well as any of the other substituents as defined for R⁵ or R⁶.

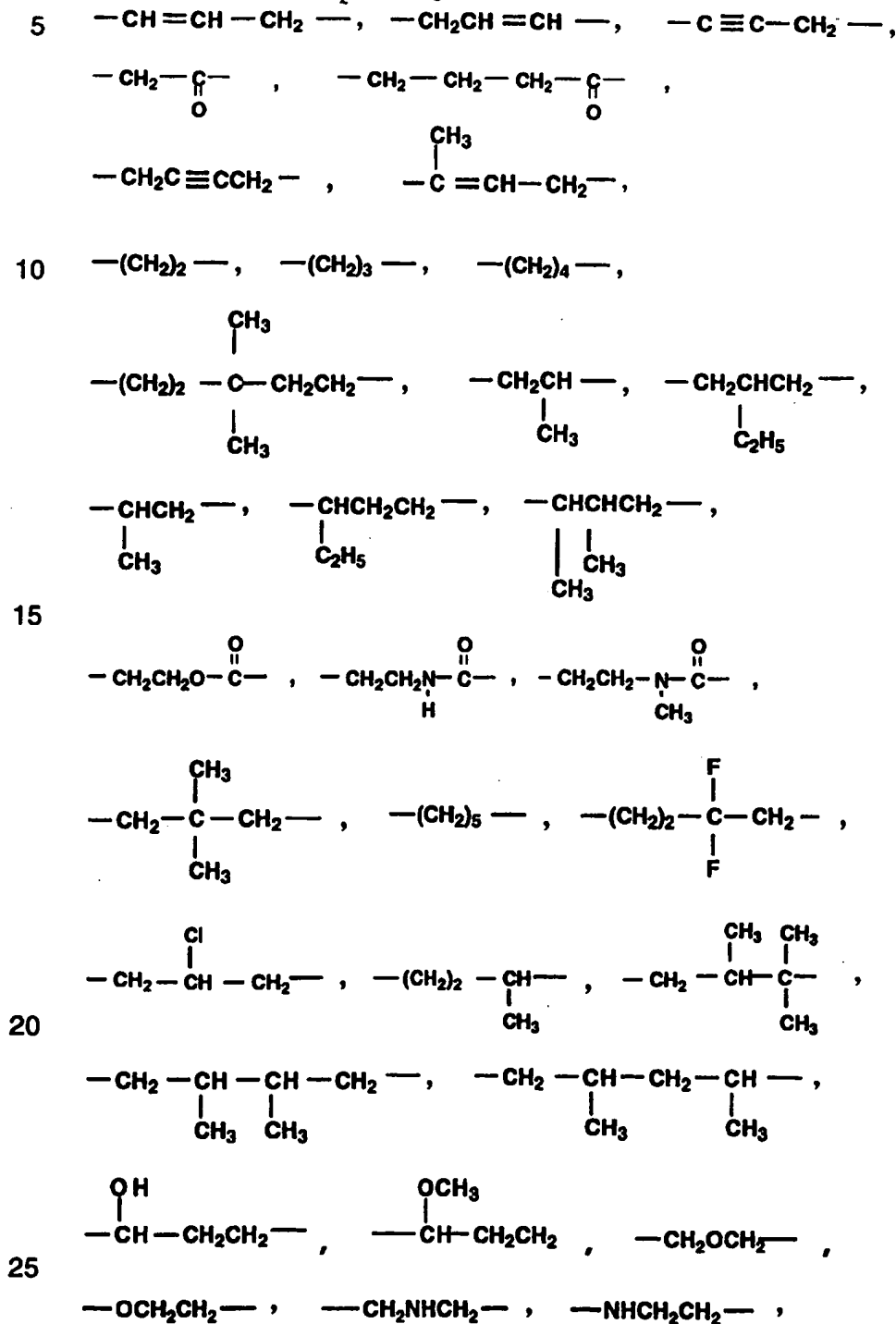
The term "alkylene" as employed herein alone or as part of another group (which also encompasses "alkyl" as part of another group such as arylalkyl or heteroarylalkyl) refers to alkyl groups as defined above having single bonds for attachment to other groups at two different carbon atoms and may optionally be substituted as defined above for "alkyl". The definition of alkylene applies to an alkyl group which links one function to another, such as an arylalkyl substituent.

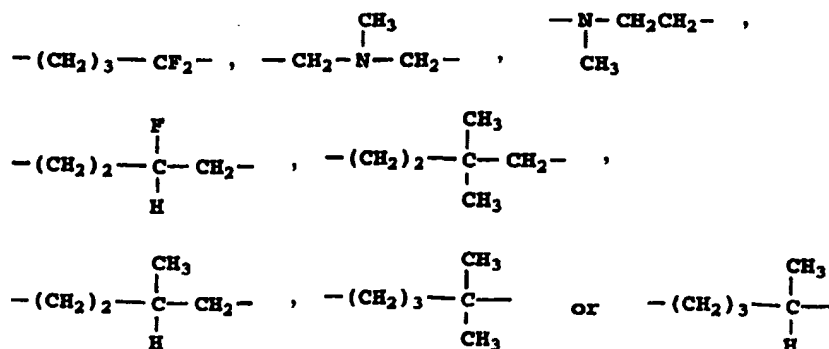
The terms "alkenylene" and "alkynylene" as employed herein alone or as part of another group (which also encompass "alkenyl" or "alkynyl" as part of another group such as arylalkenyl or arylalkynyl), refer to alkenyl groups as defined above and alkynyl groups as defined above, respectively, having single bonds for attachment at two different carbon atoms.

Suitable alkylene, alkenylene or alkynylene groups or (CH₂)_n or (CH₂)_p (which may include alkylene, alkenylene or alkynylene groups) as defined herein, may optionally include 1, 2, or 3 alkyl, alkoxy, aryl, heteroaryl, cycloheteroalkyl, alkenyl, alkynyl, oxo, aryloxy, hydroxy, halogen substituents as well as any of the substituents defined for R⁵ or R⁶, and in addition, may have one

of the carbon atoms in the chain replaced with an oxygen atom, N-H, N-alkyl or N-aryl.

Examples of alkylene, alkenylene, alkynylene, $(CH_2)_n$ and $(CH_2)_p$ groups include





5

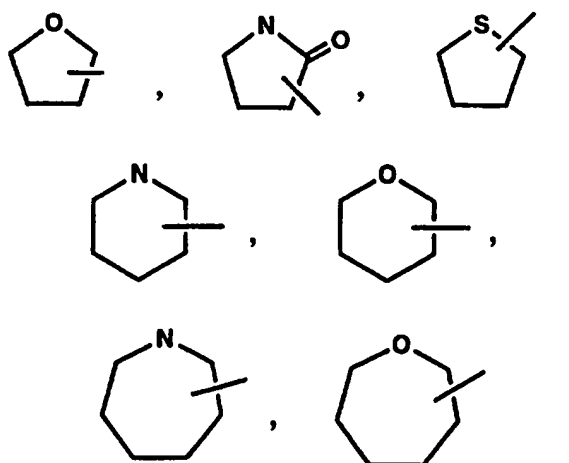
The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF₃, with chlorine or fluorine being preferred.

10

The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

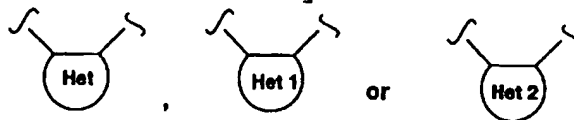
The term "cycloheteroalkyl" as used herein alone or as part of another group refers to a 5-, 6- or 7-membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker (CH₂)_p (which is defined above), such as

25

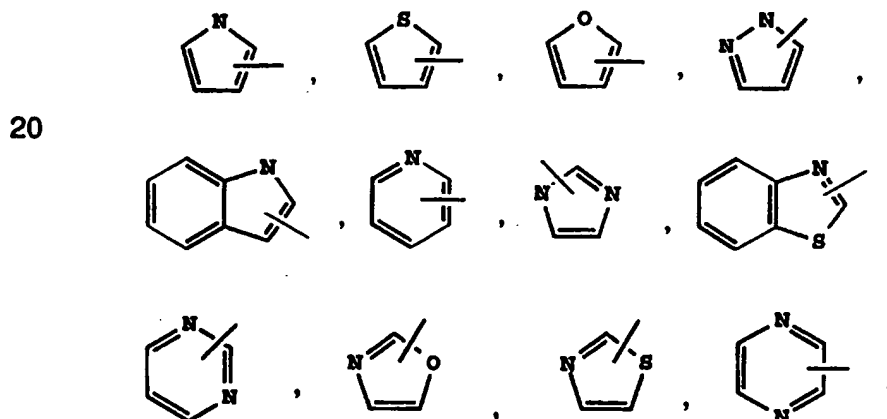


and the like. The above groups may include 1 to 3 substituents such as any of the R^1 , R^5 or R^6 groups as defined above. In addition, any of the above rings can be fused to 1 or 2 cycloalkyl, aryl, heteroaryl or cycloheteroalkyl rings.

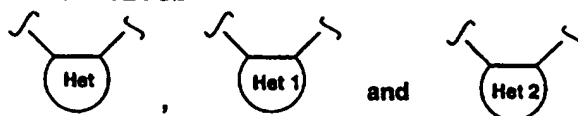
The term "heteroaryl" or



(also referred to as heteroaryl) as used herein alone or as part of another group refers to a 5- or 6- membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (which is defined above), such as

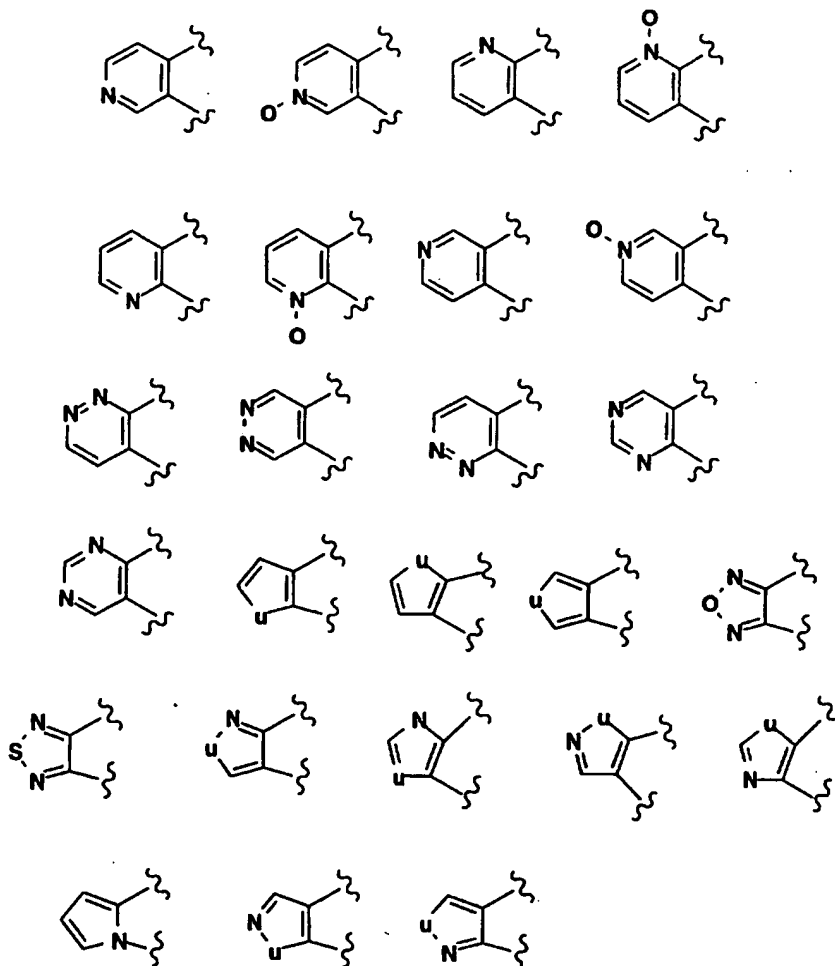


and the like, and includes all possible N-oxide derivatives.



are the same or different as defined hereinbefore and are attached to the central ring of the indenyl or fluorenyl type group at adjacent

positions (that is ortho or 1,2-positions).
Examples of such groups include



5

wherein u is selected from O, S, and NR^{7a};
R^{7a} is H, lower alkyl, aryl, -C(O)R^{7b}, -C(O)OR^{7b};
R^{7b} is alkyl or aryl, and includes all possible N-oxide derivatives.

10

The heteroaryl groups including the above groups may optionally include 1 to 4 substituents such as any of the substituents listed for aryl, or those substituents indicated for R⁵ or R⁶ groups as defined above. In addition, any of the above

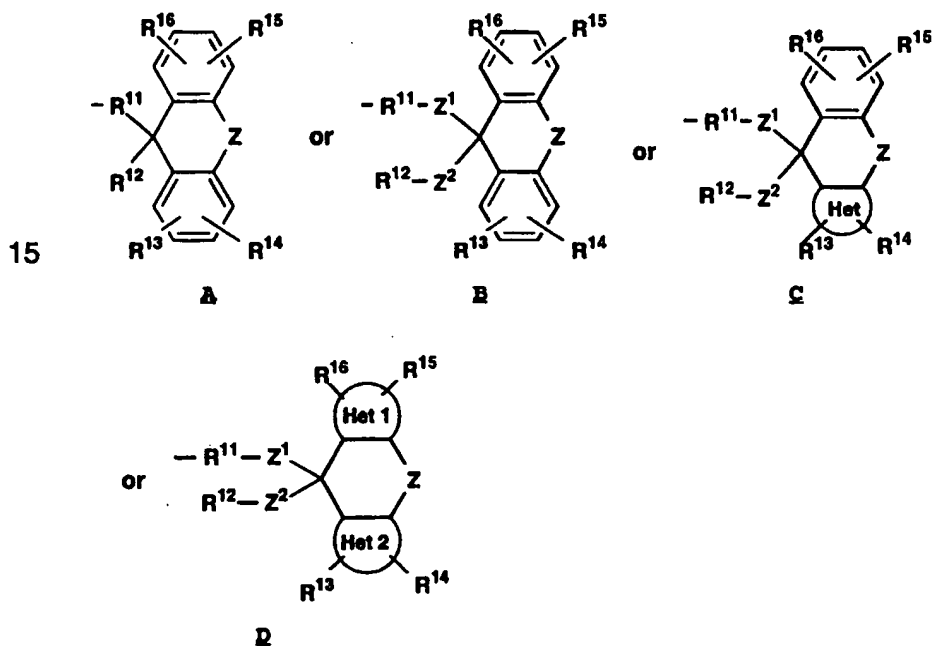
15

rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

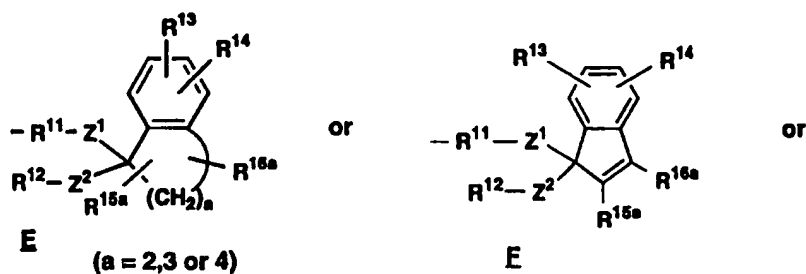
The term "cycloheteroalkylalkyl" as used herein alone or as part of another group refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to a $(\text{CH}_2)_p$ chain.

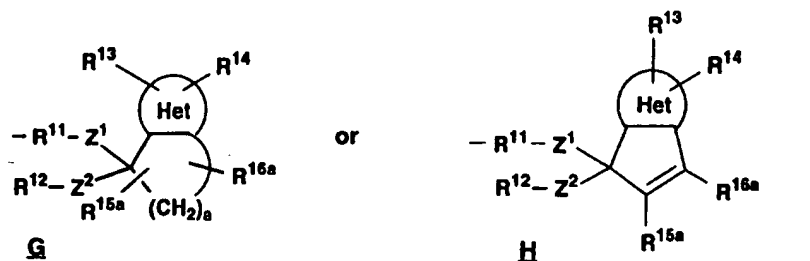
- 5 The term "heteroarylalkyl" or "heteroarylalkenyl" as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to a $-(\text{CH}_2)_p-$ chain, alkylene or
- 10 alkenylene as defined above.

The term "fluorenyl" or "fluorenyl analog" or "fluorenyl-type group" as employed herein refers to a group of the structure:



- 20 The term "indenyl-type group" as employed herein refers to a group of the structure

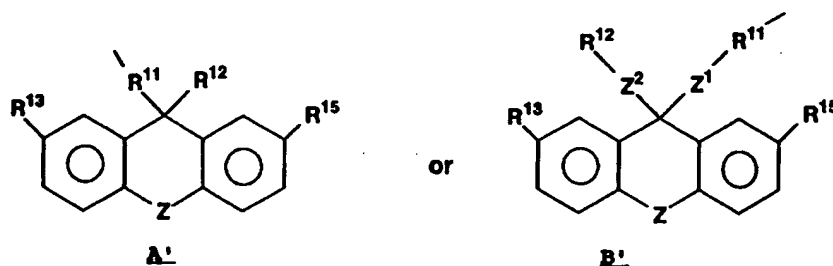




5 Z, Z¹, Z², R¹¹, R¹², R¹³, R¹⁴, R¹⁵, R¹⁶, R^{15a} and R^{16a} as used in the above groups A through H are as defined hereinbefore.

Preferred are compounds of formulae I and II wherein

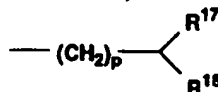
10 R¹ is arylalkyl, arylalkenyl, heteroaryl-alkyl, heteroarylalkenyl,



(including where Z¹ is a bond and R¹¹ is alkylene

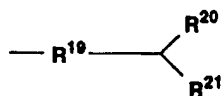
15 or alkenylene and Z² is —NH—C(=O)—S(=O)— , (S(=O))_2 or C(=O)— , and R¹² is C₁-C₃ alkyl or 1,1,1-trifluoroethyl, R¹³ is H or F and R¹⁵ is H or F, and Z is a bond or O; and where R¹¹ is alkylene or alkenylene or alkylene substituted with oxo, R¹² is alkyl, alkenyl,

20 aralkyl, aralkenyl, Z is O, S or a bond); or



(wherein R¹⁷ and R¹⁸ are each independently alkyl, alkenyl, aryl, arylalkyl, heteroaryl, heteroaryl-alkyl, cycloalkyl or cycloalkylalkyl); or

25



wherein R¹⁹ is aryl or heteroaryl;

R²⁰ is aryl or heteroaryl;

R²¹ is alkyl, aryl, alkylaryl, arylalkyl
 5 aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl,
 heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or
 cycloalkylalkoxy.

In structure I, it is preferred that R², R³
 and R⁴ are each H and X is CH₂, CH₂CH₂, or CH=CH.

10 In structure II, it is preferred that R⁶ is
 H or CH₃ and R⁵ is cycloalkyl, phenyl, aryl or
 heteroaryl, or cycloalkyl, phenyl, aryl heteroaryl
 having an ortho hydrophobic substituent which is
 alkyl, alkoxy, haloalkyl (containing up to five
 15 halo groups), trifluoromethyl, aryl, aryloxy,
 arylalkyl, arylalkoxy, haloalkoxy (containing up
 to five halo groups).

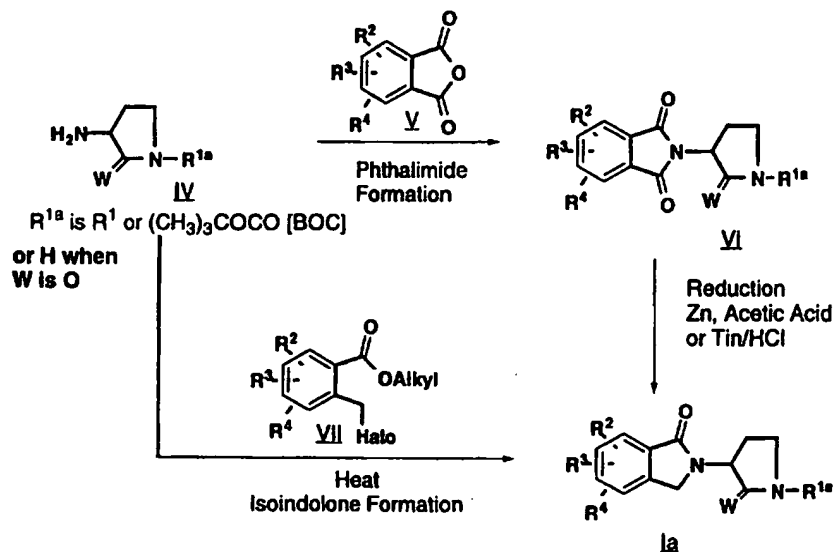
In structure II, it is also preferred that
 R¹ is arylalkyl or heteroarylalkyl wherein alkyl of
 20 each has at least 2 carbons (preferably at least 3
 carbons) and R⁵ and R⁶ may be as defined
 hereinbefore and may or may not be the preferred
 groups set out above.

It is to be understood that combinations of
 25 substituents which lead to chemically unstable
 molecules are not included within the scope of the
 present invention; for example, compounds of the
 invention will not include -O-O-, -O-C-OH, N-C-OH
 and -S-C-OH linkages.

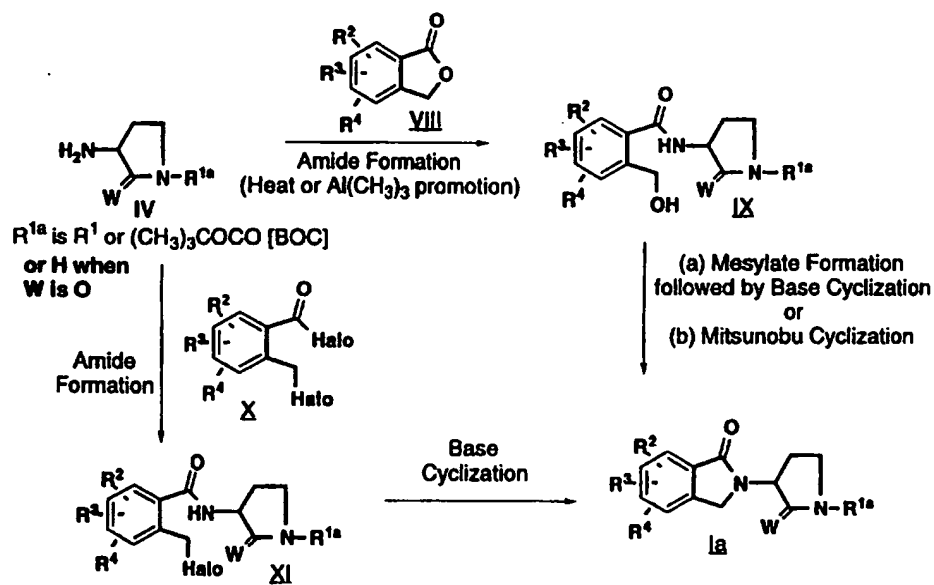
30 The compounds of formulae I and II may be
 prepared by the exemplary processes described in
 the following reaction schemes. Exemplary reagents
 and procedures for these reactions appear
 hereinafter and in the working Examples.

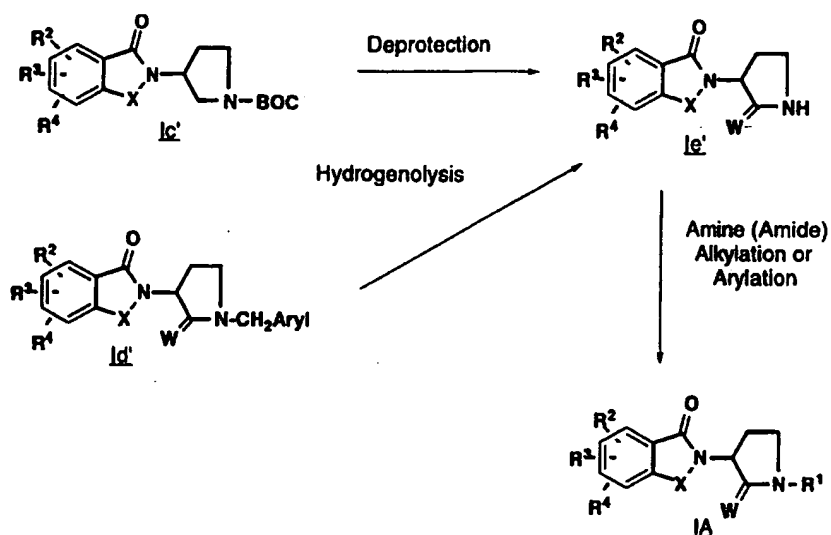
35

Scheme I. Routes to Isoindolinone Piperidines

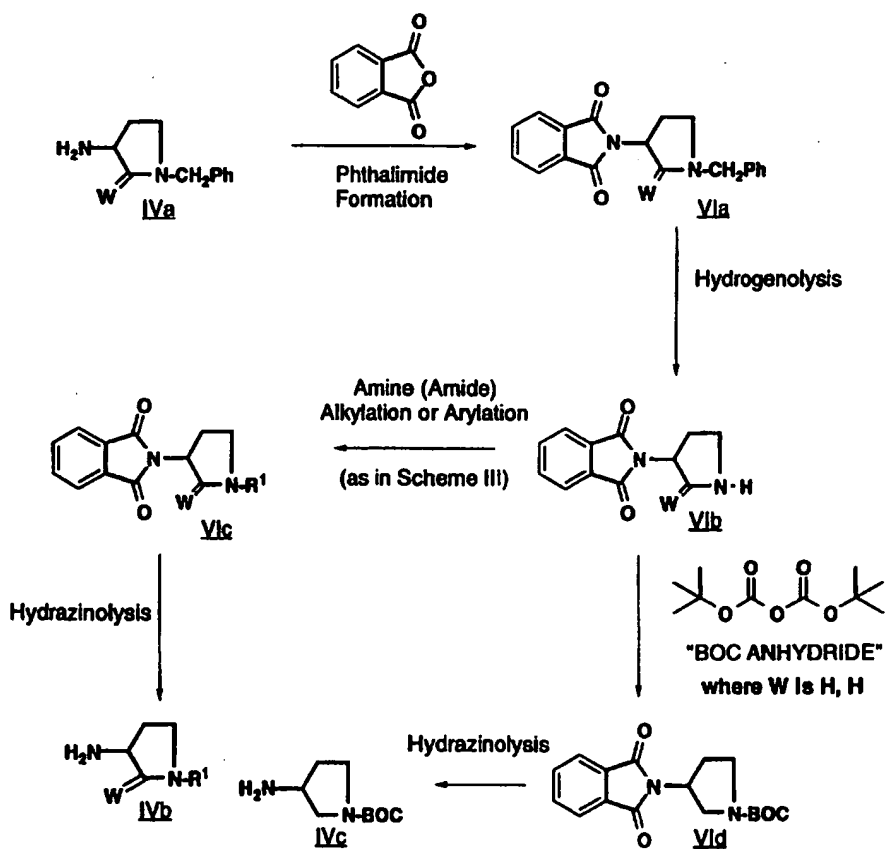


Scheme II. Additional Routes to Isoindolinone Piperidines

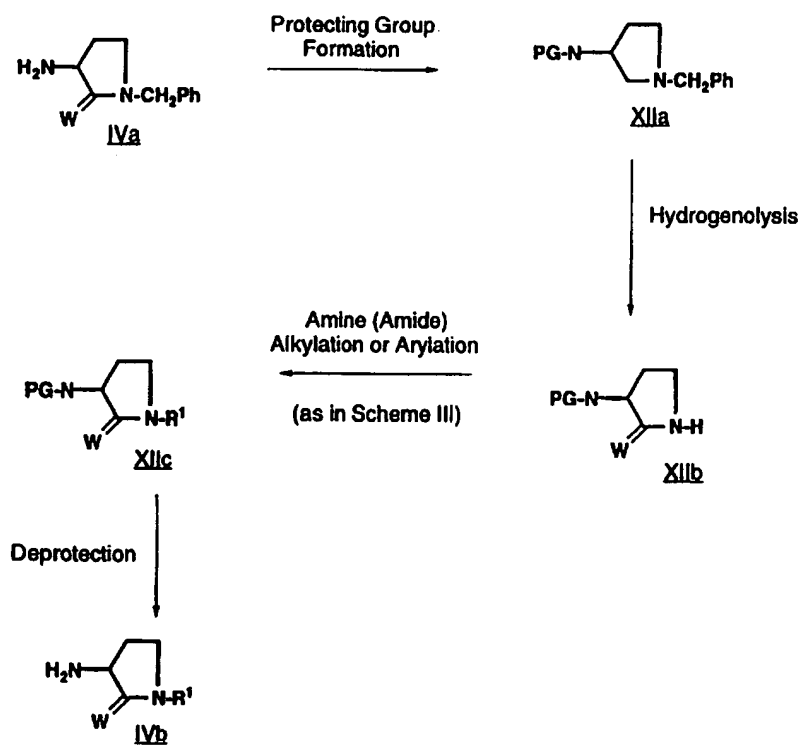


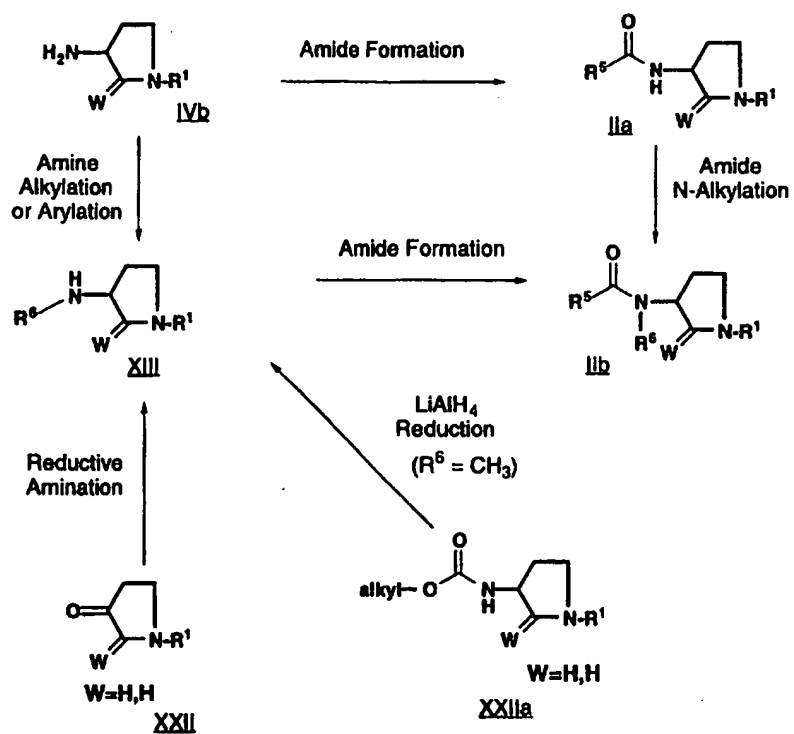
Scheme III. Introduction of R¹ by Alkylation or Arylation

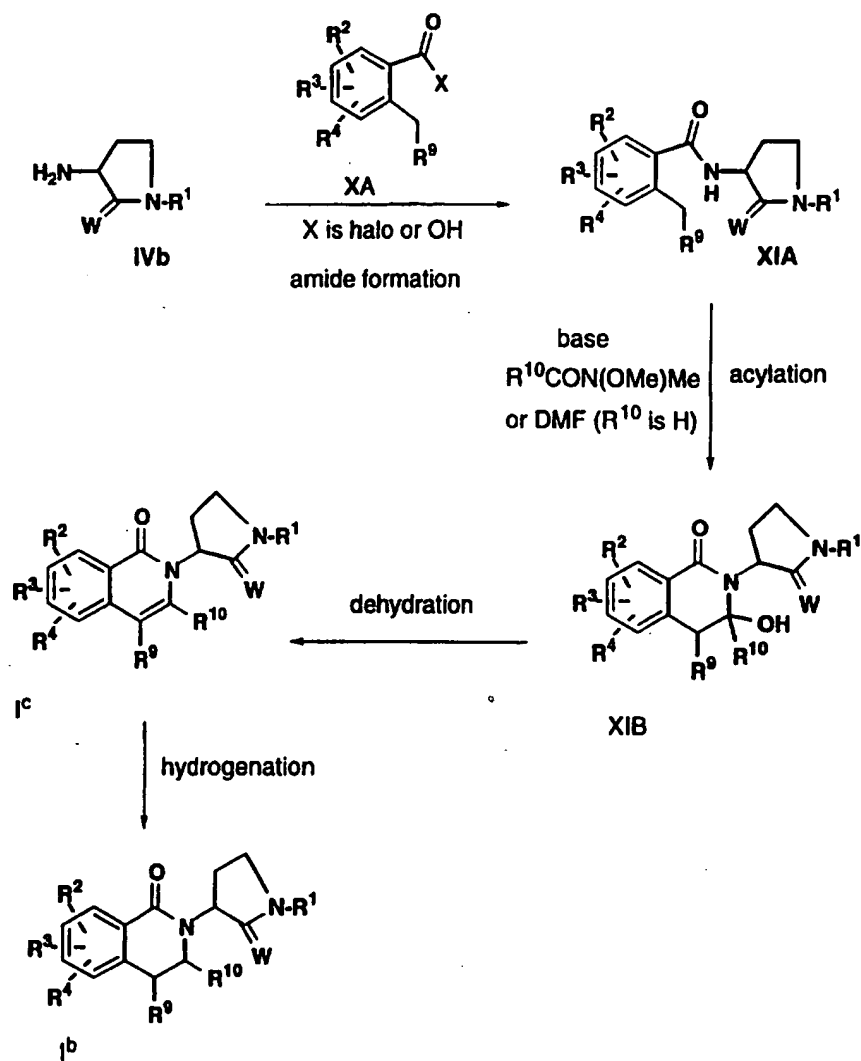
Scheme IV. Routes to Starting Materials IVb and IVc

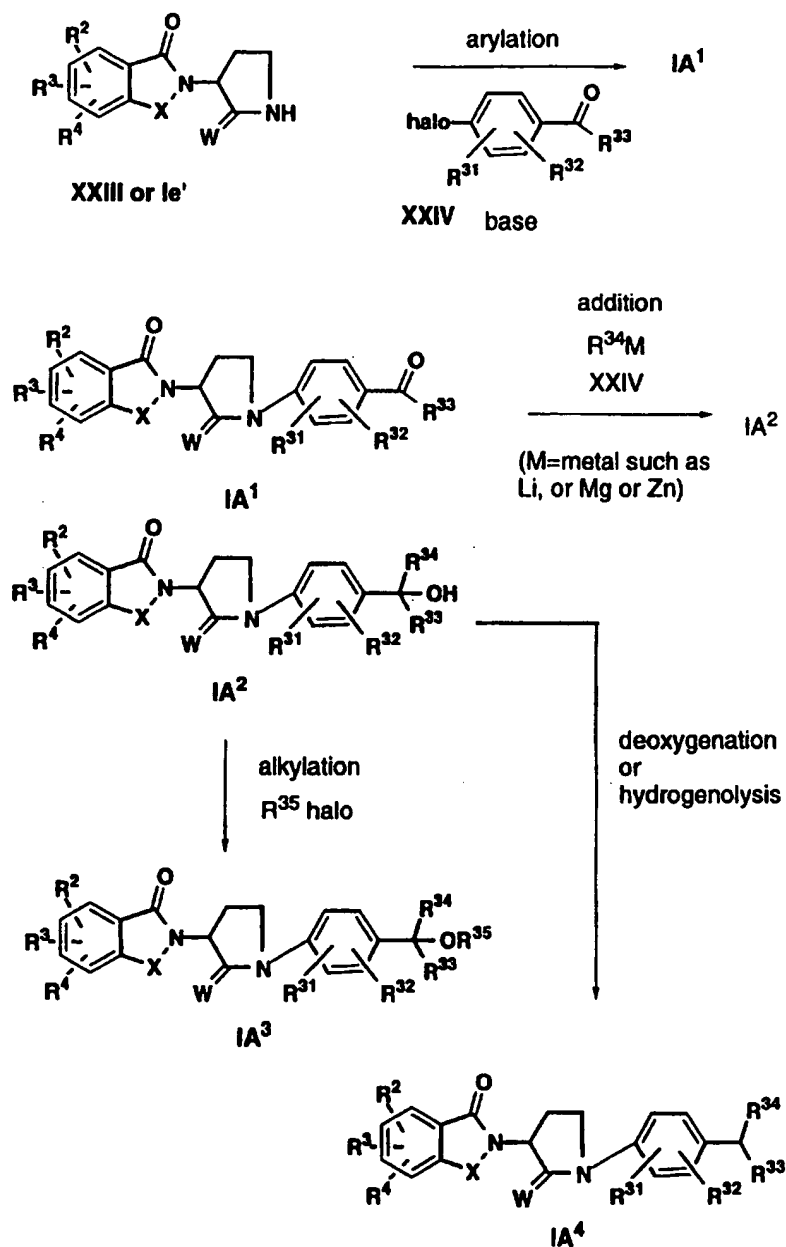


Scheme V. General Routes to Starting Materials IVb



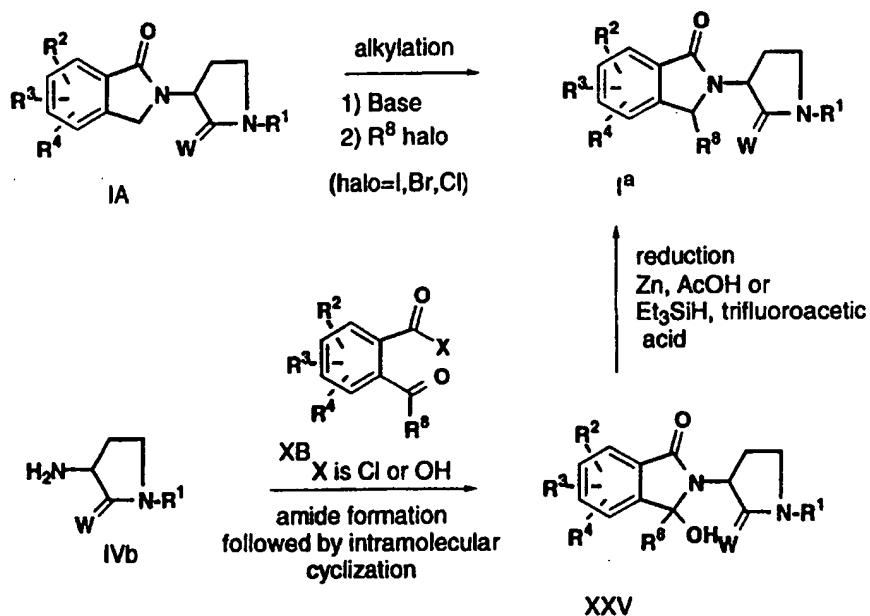
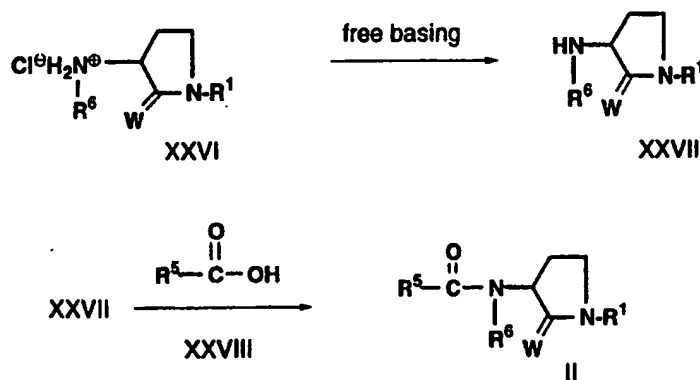
Schemes VI and VII. General Routes to II

Scheme VIII Preparation of Compounds I^b, I^c

Scheme IX Preparation of Compounds IA¹-IA²

R³¹ and R³² are independently selected from any of the R², R³, or R⁴ radicals;

- 5 R³³ and R³⁴ are independently selected from any of the R¹ radicals as well as aryloxy, alkoxy, arylalkoxy, heteroarylalkoxy and heteroaryloxy;
- R³⁵ can be any of the R¹ radicals.

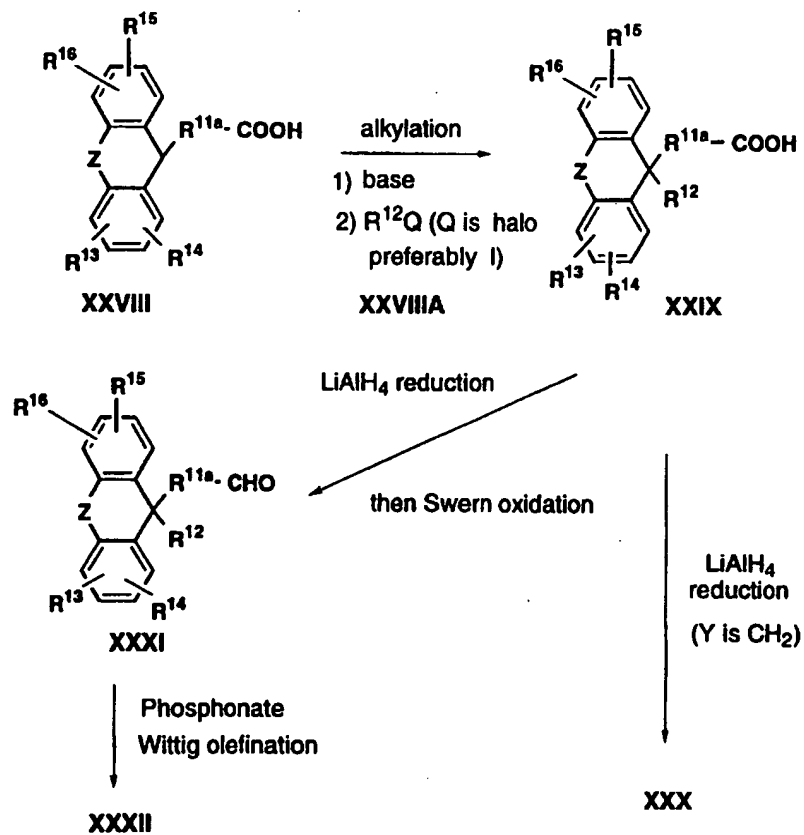
Scheme X Preparation of Compound I^aScheme XI Preparation of Compound II
(Robotic Amide Coupling)

5 In the following Schemes XII et al, in the fluorenyl rings or fluorenyl analogs, the fused aryl groups:

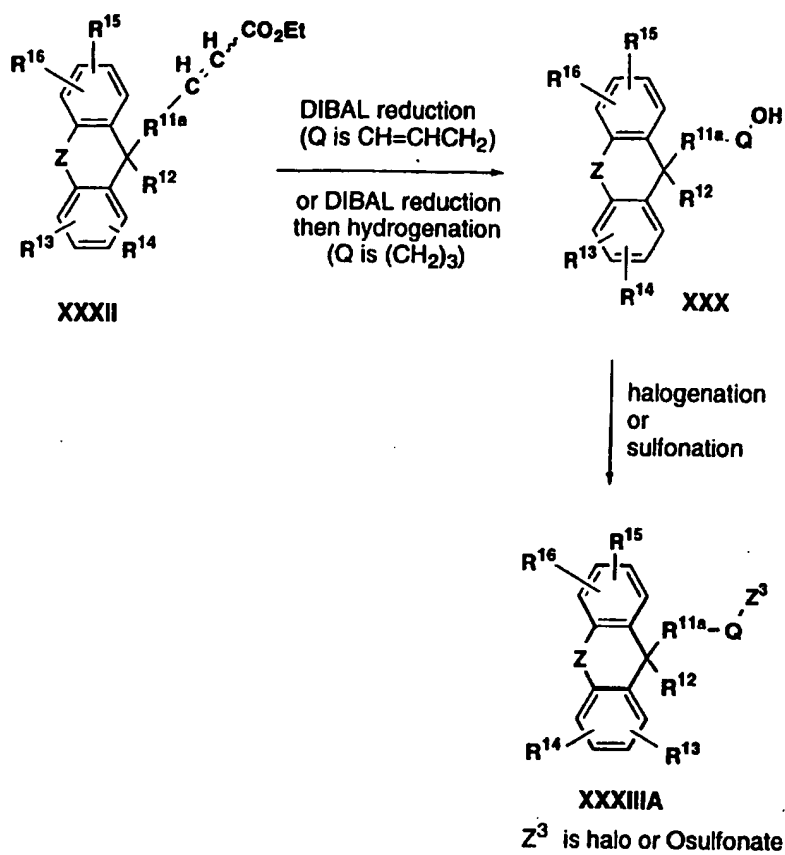


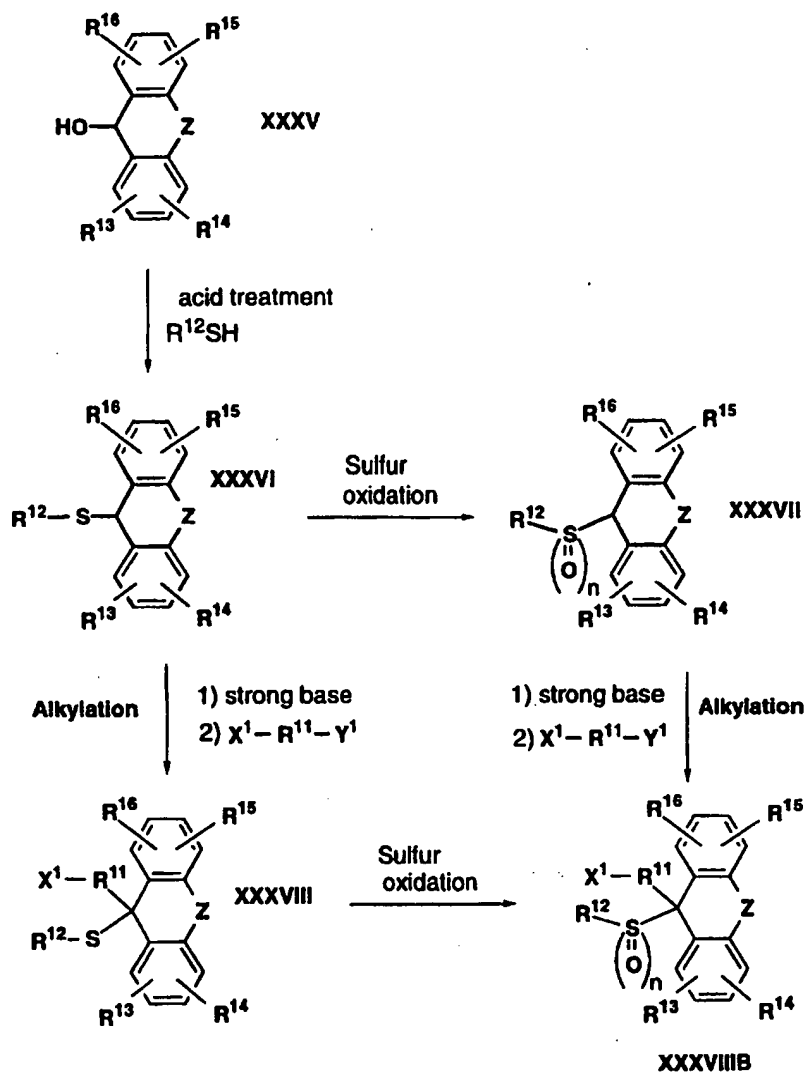
may each optionally be replaced by a 5- or 6-membered heteroaryl ring as defined herein.

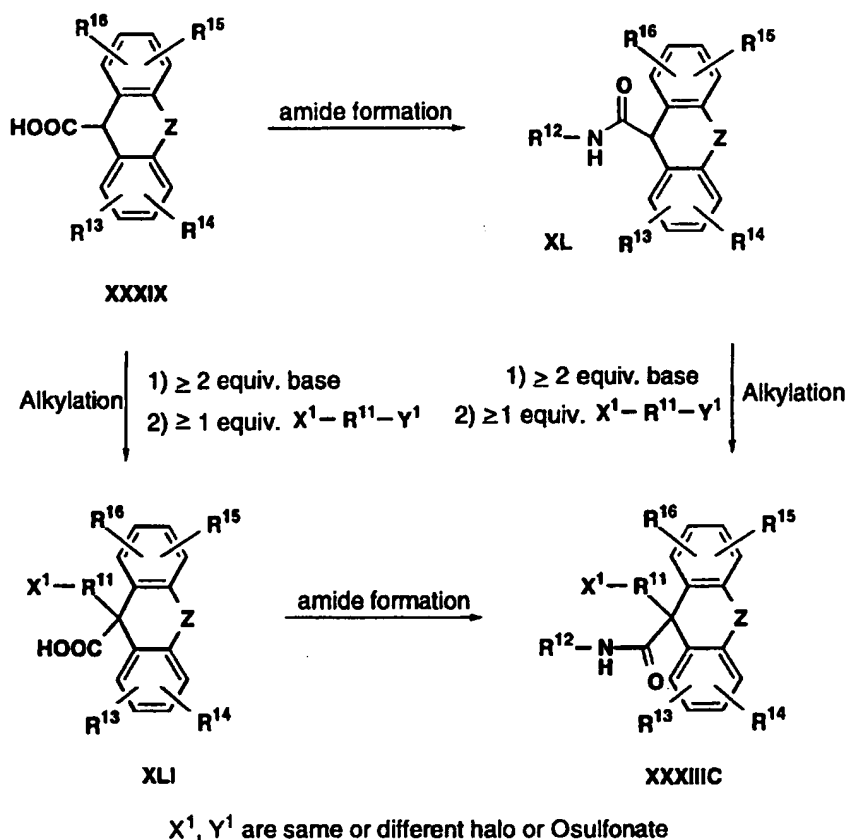
Scheme XII



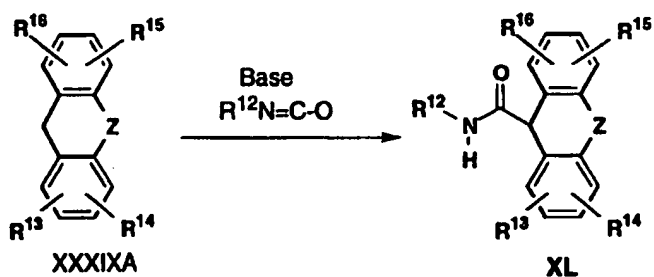
5 R^{11a} can be any of the R^{11} radicals.



Scheme XIII - Preparation of Intermediates where Z^2 is S, SO or SO_2 

Scheme XIVA - Preparation of A (Intermediates where Z^2 is NHCO)**Scheme XIVB**

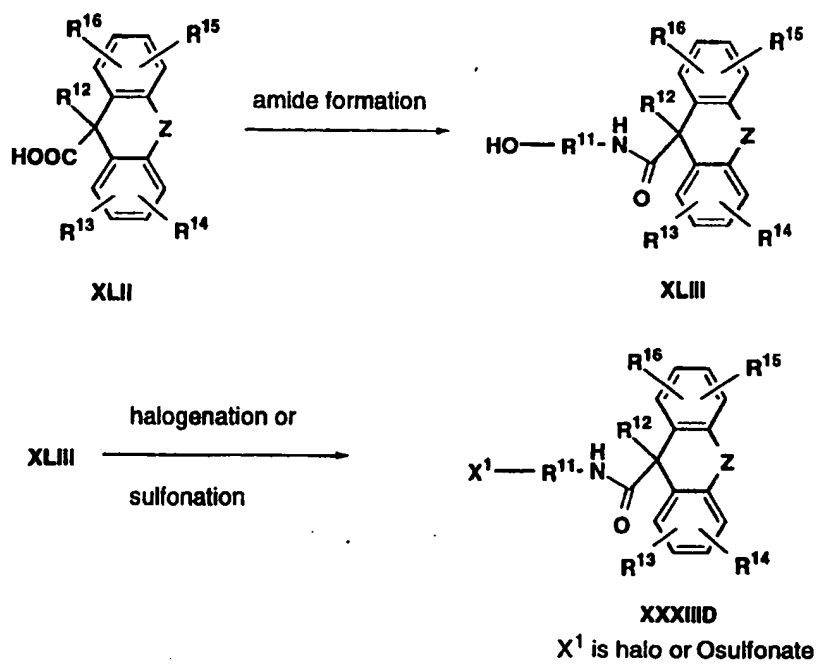
Alternative Procedure for Preparing Intermediate XL
(Shown in Scheme XIVA)



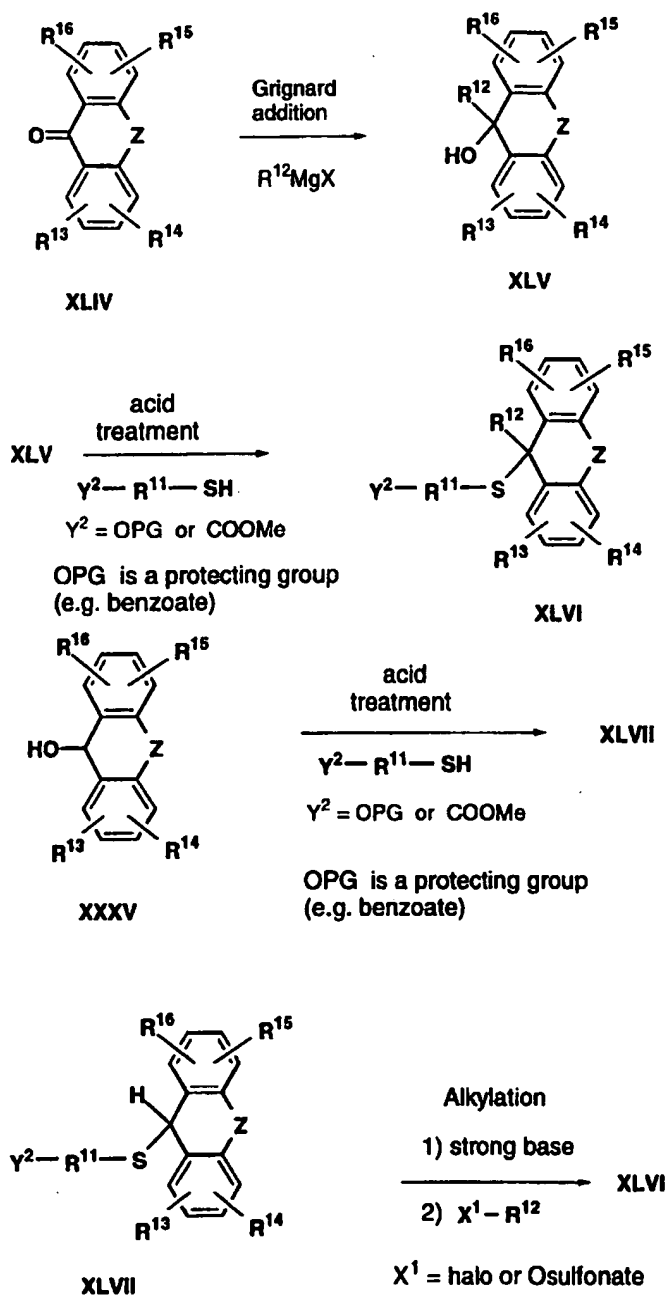
In carrying out the above reaction, bases such as *n*-butyllithium, lithium bis(trimethylsilyl) amide and sodium bis(trimethylsilyl) amide may be employed in an aprotic solvent such as THF, at between -78°C and 35°C .

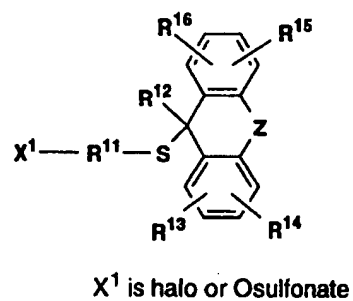
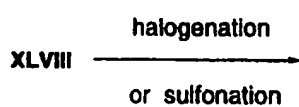
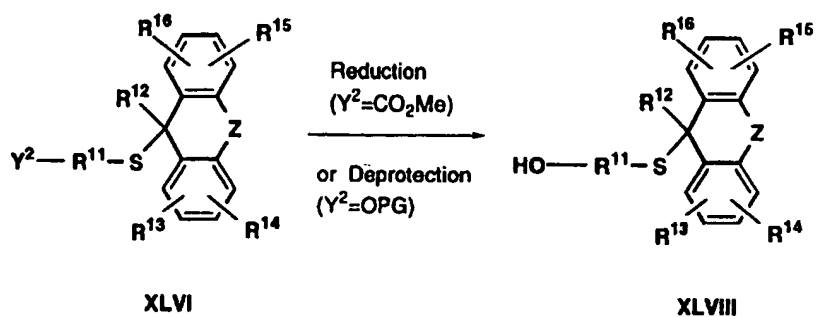
It is preferable to have the starting material and isocyanate ($R^{12}N=C=O$) together in solvent, and then add the base, and optionally add further excess isocyanate subsequently.

Scheme XV - Preparation of Intermediate where Z^1 is $\begin{array}{c} \text{H} \\ | \\ -\text{N}-\text{C}- \\ || \\ \text{O} \end{array}$

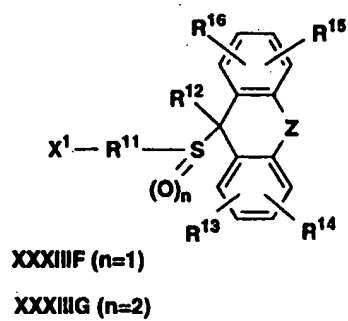
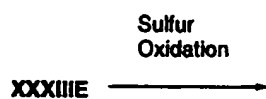


Scheme XVI

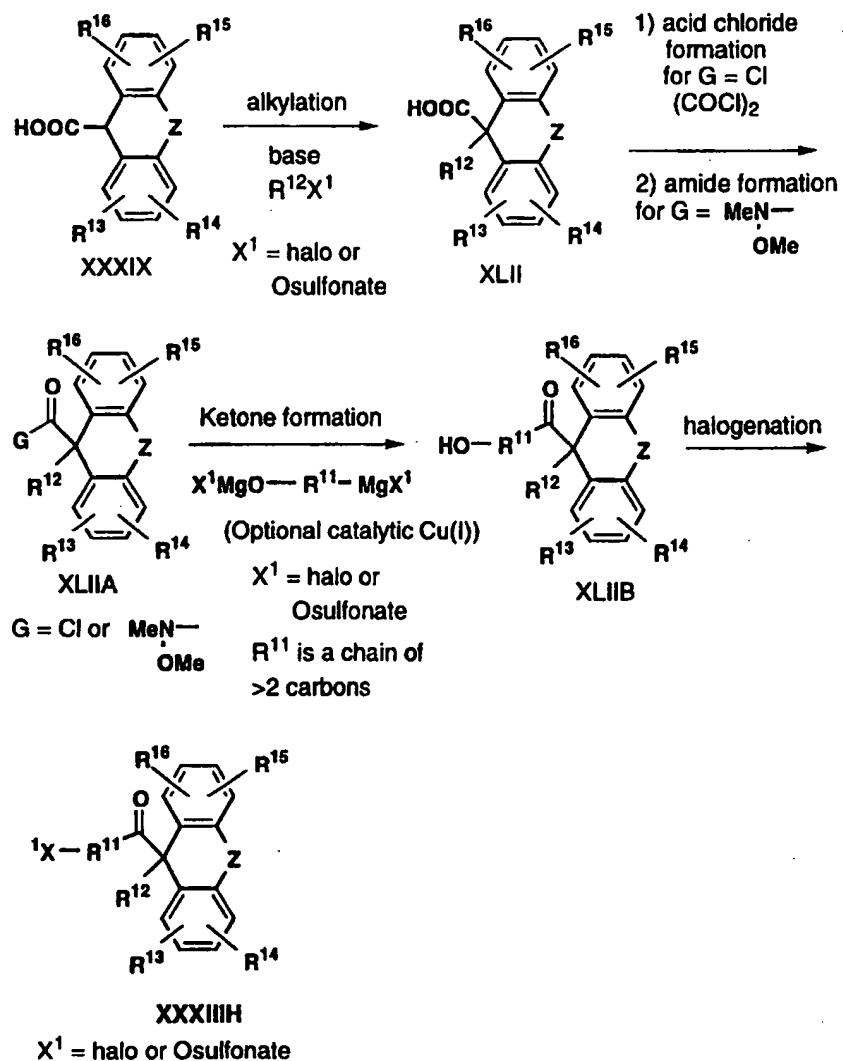


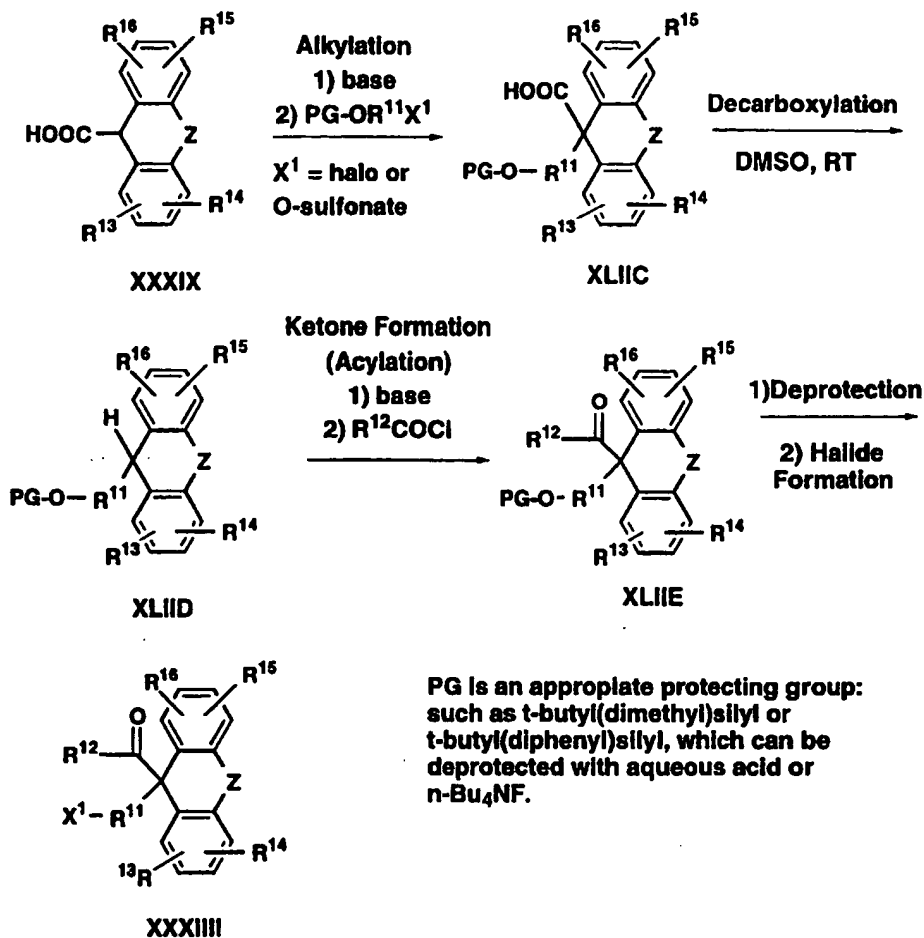


5

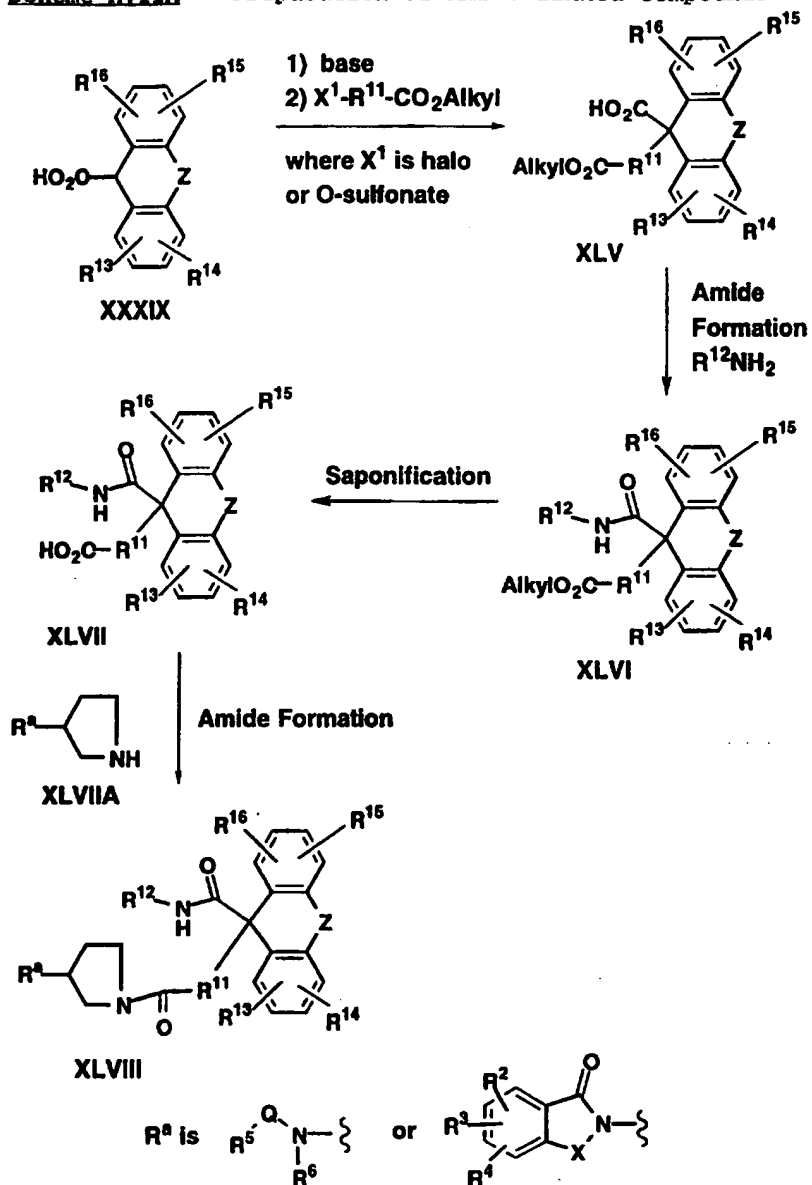


Scheme XVIA Preparation of Ketones

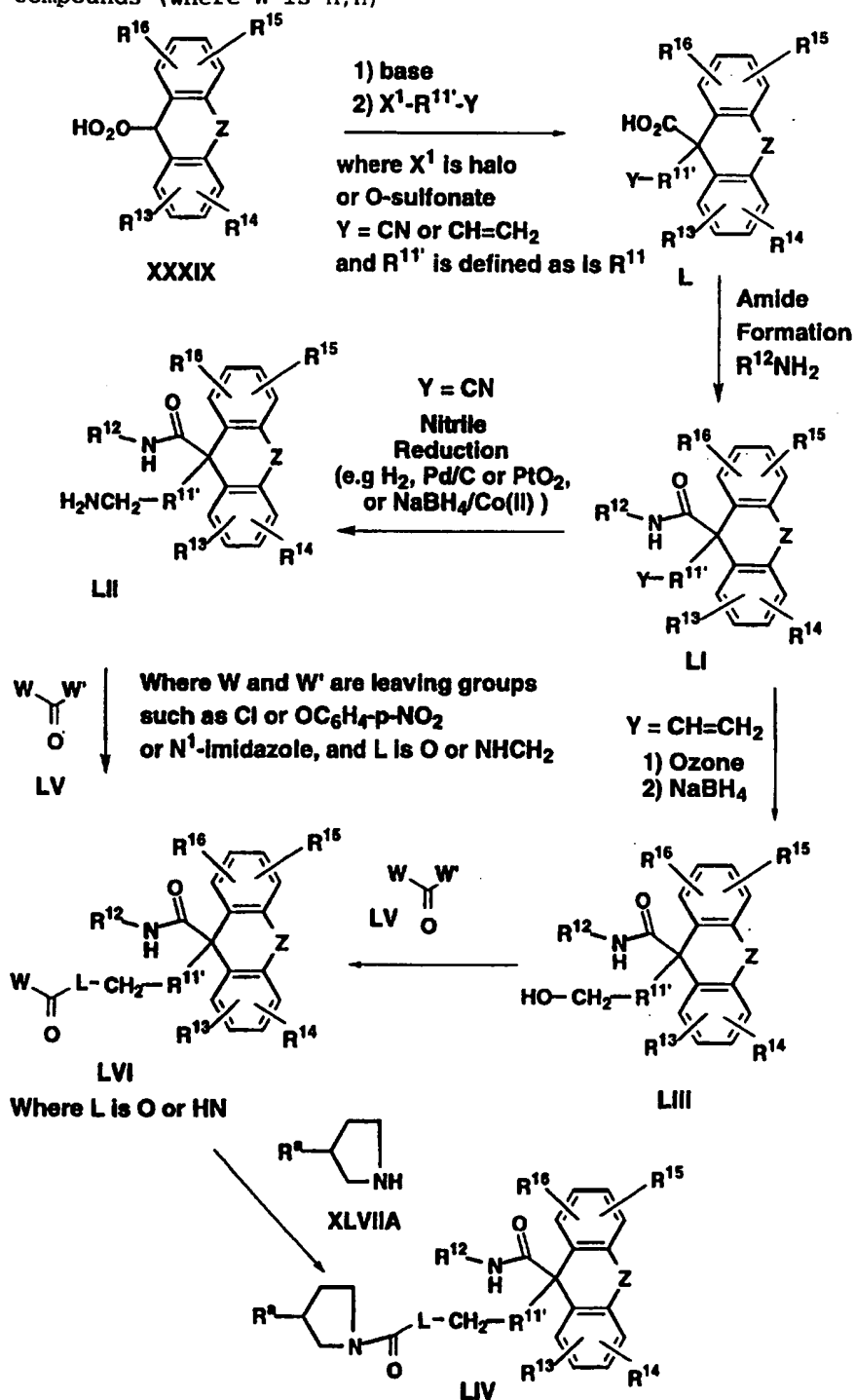


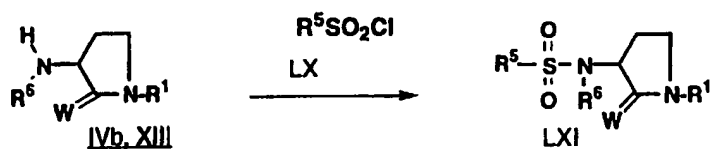
Scheme XVIB. Preparation of Ketones (Preferred Route)

Scheme XVIIIA - Preparation of Amide Linked Compounds

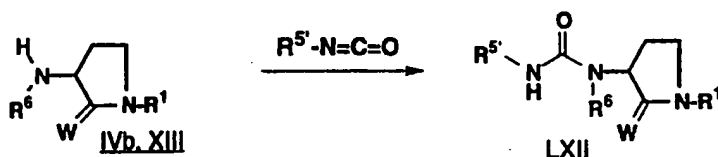


Scheme XVIIIB - Preparation of Carbamate and Urea Linked Compounds (where W is H, H)



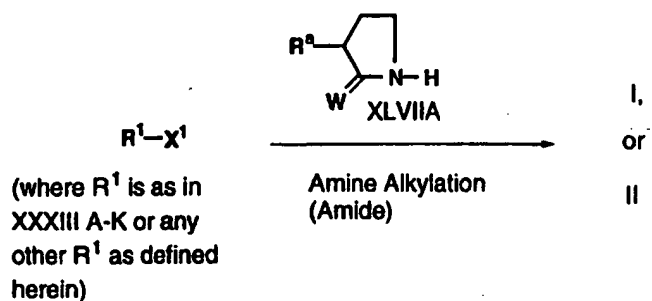
Scheme XVIIIA - Formation of Sulfonamides

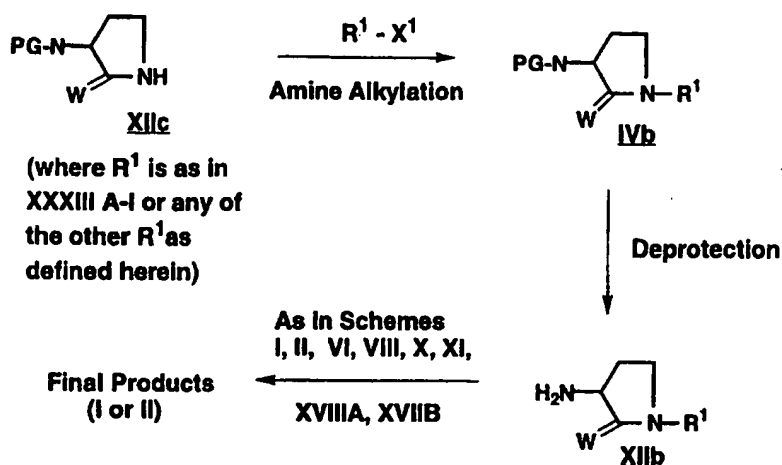
(Reaction in a variety of solvents (CH_2Cl_2 , THF, pyridine) optionally in the presence of a tertiary amine base, such as pyridine or triethyl amine).

5 Scheme XVIIIB - Formation of Ureas (R^5 is Amino)

(1 to 10 equiv of $\text{R}-\text{C}=\text{N}=\text{O}$, in aprotic solvent such as toluene, from 0°C to 150°C).

(R^5' is alkyl, aryl, heteroaryl or arylalkyl).

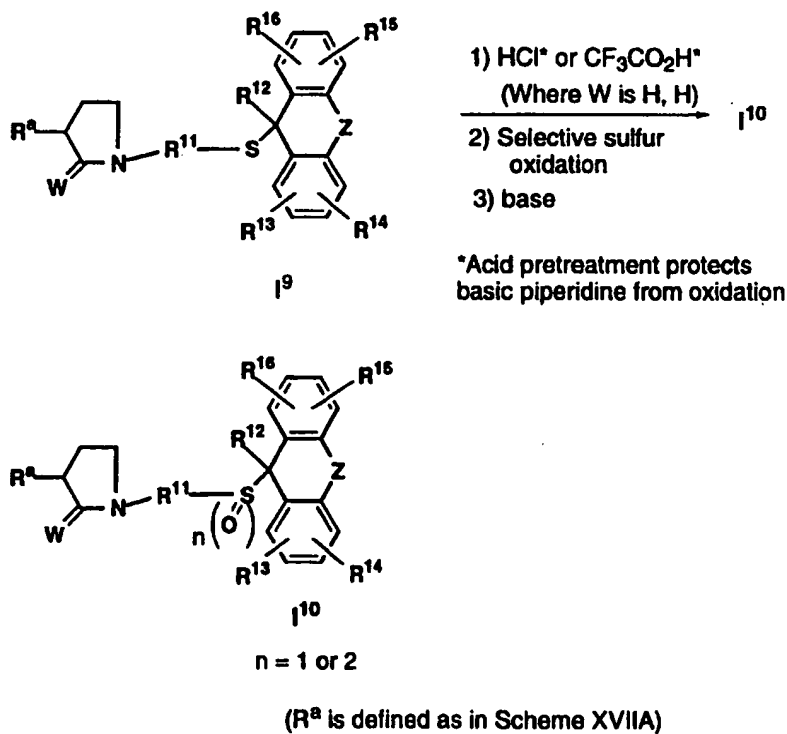
10 Scheme XIXA - General Route to Final Product

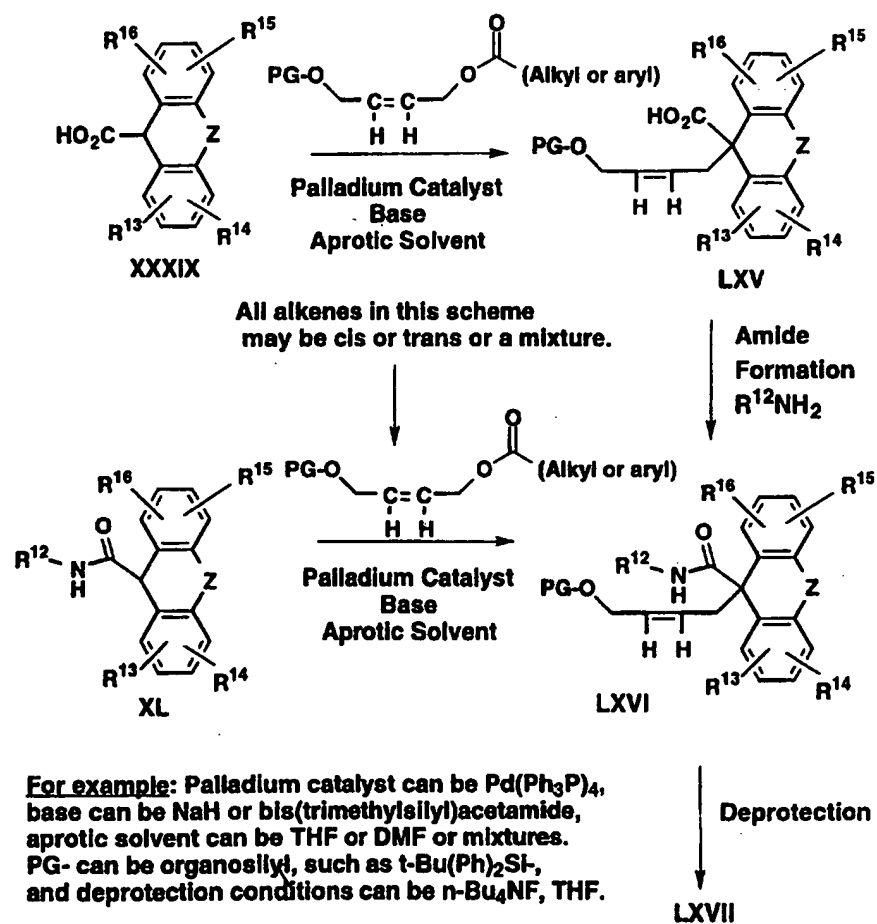
Scheme XIXB General Route to Final Products (I or II)

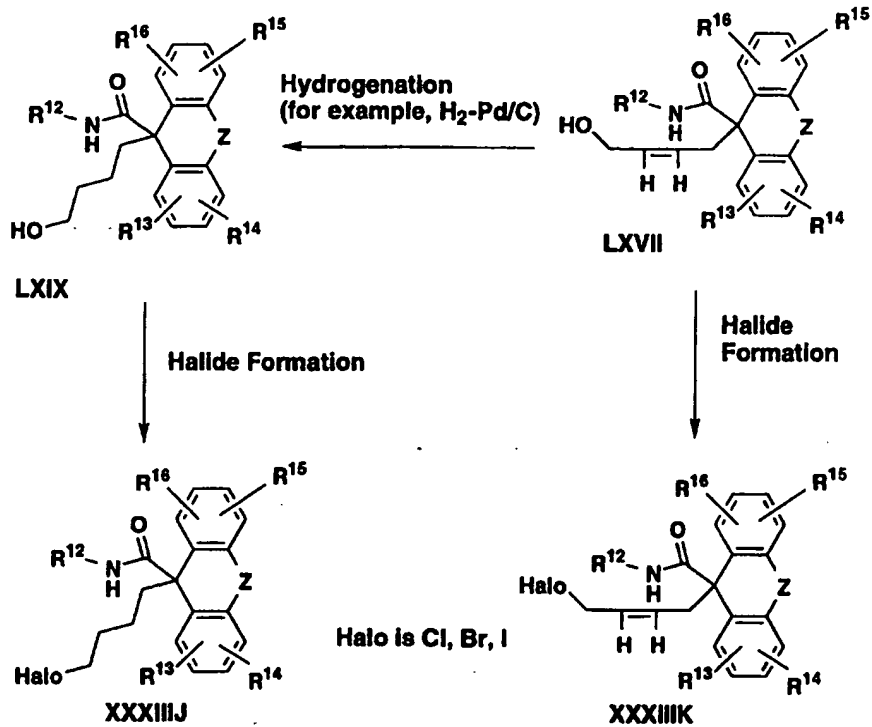
(Example of a protected nitrogen (PG-N) is the t-BuOC=ONH (BOC amino) group, which can be deprotected under mild conditions, such as anhydrous HCl in dioxane or neat trifluoroacetic acid).

Scheme XX - Oxidation of sulfur at the end of the reaction sequence

5

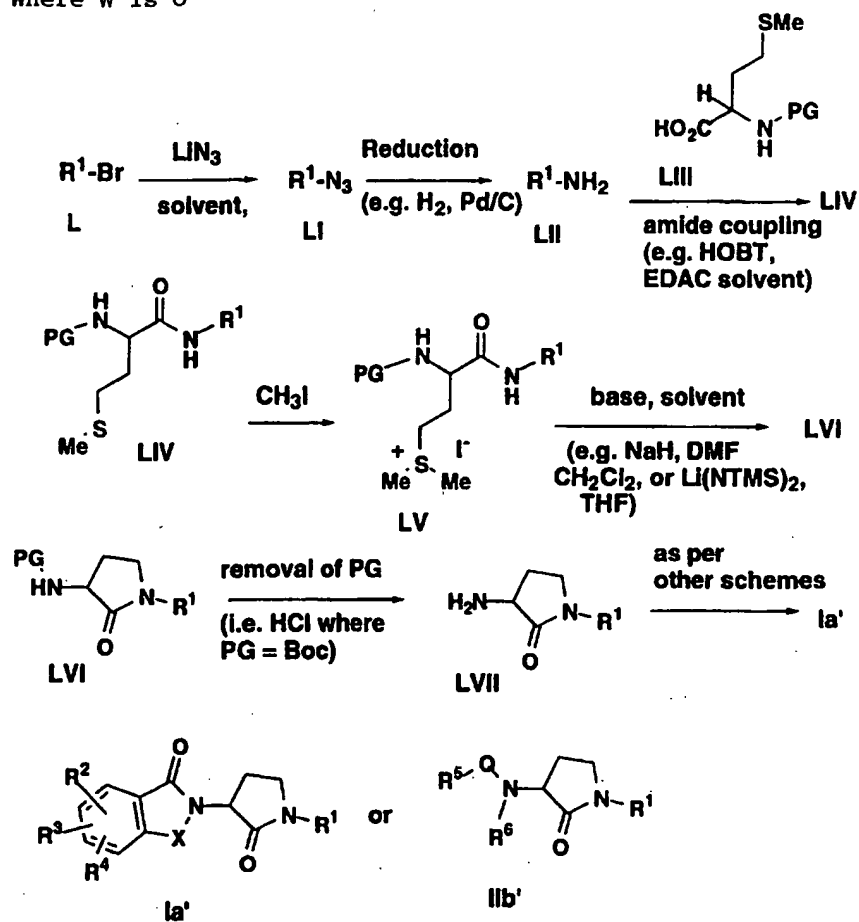


Scheme XXI - Preparation of Halide Intermediates

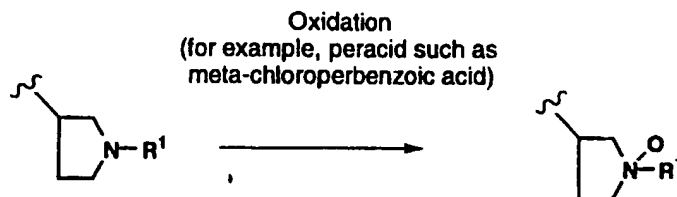


Scheme XXII - Preparation of Formulae I and II Compounds

Where W is O



Scheme XXIII - Preparation of N-Oxides of Formulae I and II
Compounds



5

In the above Reaction Schemes XII through
XXI, the starting fluorenyl-type acid XXVIII,
alcohol XXXV, acids XXXIX and XLII, ketone XLIV,
hydride XXXIXA, and amide XL groups may be
10 substituted with corresponding acid, alcohol,
ketone, hydride and amide containing fluorenyl
type groups as set out in A, B, C and D or
indenyl-type groups as set out in E, F, G and/or H
to provide an intermediate compound for use in
15 preparing a compound of formula I or II of the
invention as per Reaction Schemes I to XXII.

Phthalimide formation (Reaction Schemes I,
IV and XXII) may be carried out by heating to
about 80 to 150°C in an oil bath optionally in an
20 inert solvent or by various other procedures known
in the art.

Reduction (Reaction Schemes I, XXII) may be
carried out by treatment with such reducing agents
as zinc in the presence of acetic acid or tin in
25 the presence of hydrochloric acid under an inert
atmosphere (e.g., argon).

Isoindolone formation (Reaction Schemes I,
XXII) may be carried out by heating in the range
of about 50 to 150°C in an organic solvent (e.g.,
30 toluene, ethanol, dimethylformamide) optionally in
the presence of a salt (e.g., potassium carbonate)
or a tertiary amine base (e.g., 2,6-di-*t*-butyl-
pyridine or triethylamine).

Amide formation (Reaction Schemes II, VI, VII, VIII, X, XI, XIVA, XV, XVI, XVIA, XVB, XVIIA, XVIIB, XXI, XXII), may be carried out by a number of methods known in the art. For example,

5 an amine substrate may be treated with (1) an acid halide $R^5C(O)halo$ or compound X or XA in an aprotic solvent, optionally in the presence of a tertiary amine base (e.g., triethylamine); (2) the acid halide in the presence of an aqueous base under

10 Schotten-Baumann conditions; (3) a free carboxylic acid (R^5CO_2H) in the presence of a coupling agent such as dicyclohexylcarbodiimide (DCC), diisopropyl carbodiimide (DIC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

15 (WSC), optionally in the presence of 1-hydroxybenzotriazole (HOBT); (4) the free acid in the presence of N, N-carbonyldiimidazole in an aprotic organic solvent followed by the amine substrate; (5) trialkylaluminum (e.g., $Al(CH_3)_3$) in an aprotic

20 solvent, followed by an ester (e.g., R^5CO_2alkyl or compound VIII) or (6) mixed anhydride formation, by reacting the acid with an acid chloride (e.g., isobutyl chloroformate or bis-(2-oxo-3-oxazolidinyl)phosphinic chloride (Bop-Cl)) in the

25 presence of a tertiary amine base (e.g., triethylamine) followed by treatment with the amine substrate.

Mesylate formation (Reaction Scheme II) may be carried out by treatment of the amine-alcohol

30 substrate with methanesulfonyl chloride and triethylamine or pyridine or in an aprotic solvent, such as dichloromethane.

Base cyclization (Reaction Schemes II, VIII, XXII) may be carried out by treatment with a

35 base (e.g., potassium *t*-butoxide, lithium hexamethyldisilazide ($LiN(TMS)_2$) or sodium hydride) in an inert solvent (e.g., dimethylformamide,

tetrahydrofuran, dimethoxymethane, or toluene). Mitsunobu cyclization (Reaction Scheme II) may be carried out by procedures generally known in the art. See, e.g., R. K. Olsen, J. Org. Chem., **49**, 3527 (1984); Genin, M. J., et al., J. Org. Chem., **58**, 2334-7 (1993).

Alternatively, a mixture of compounds IV and VIII can be converted to compound Ia in a single pot by heating the mixture in a protic solvent (e.g., water, methanol, ethenyl or isopropanol or mixtures thereof) at 100 to 200°C. See, e.g., European patent application 81/26,749, FR 2,548,666 (1983).

Protection and deprotection (Reaction Schemes III, IV, V, XVI, XVII, XIXB, XXI, XXII) may be carried out by procedures generally known in the art. See, for example, T. W. Greene, Protecting Groups in Organic Synthesis, Second edition, 1991. PG in Scheme V denotes a nitrogen-protecting group. One particularly useful group is tert-butoxycarbonyl (BOC) which can be derived from the associated anhydride as shown in Scheme IV. BOC-protected amines may typically be deprotected by treatment with acid (e.g., trifluoroacetic acid or hydrochloric acid) in procedures well understood by those having ordinary skill in the art.

Hydrogenolysis (Reaction Schemes III, IV, V) may be carried out with H₂ using a balloon apparatus or a Parr Shaker in the presence of a catalyst (e.g., palladium on activated carbon).

Amine/Amide alkylation and arylation (Reaction Schemes III, IV, V, IX, XII, XIXA, XIXB) may be carried out by methods known in the art. Suitable procedures are described in Cortizo, L., J. Med. Chem. **34**, 2242-2247 (1991). For example, the alkylation or arylation may be carried out by

treating the amine substrate with a halide (e.g., R¹-halo) or an oxytosylate (e.g., R¹-O-tosylate) in an aprotic solvent (e.g., dimethylformamide), optionally in the presence of a tertiary amine (e.g., triethylamine), an inorganic base (e.g., potassium carbonate, NaH), or lithium hexamethyldisilazide).

Reductive amination may be employed as an alternative to the foregoing amine alkylation and arylation procedures where W is H, H when R¹, R⁶ or R⁷ is R⁹R¹⁰CH- and R⁹ and R¹⁰ are each independently hydrogen, alkyl, alkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl, or R⁹ and R¹⁰ together are alkylene (i.e., R⁹R¹⁰CH- forms a cycloalkyl group). Such reductive amination may be carried out by treating the amine with (a) a ketone or aldehyde (R⁹-C(O)-R¹⁰), (b) NaBH₄, NaBH₃CN or NaB(acetoxy)₃H, (c) a protic solvent (e.g., methanol) or a dipolar aprotic solvent (e.g., acetonitrile), and, optionally, (d) an acid (e.g., acetic acid, trifluoroacetic acid, hydrochloric acid, or titanium isopropoxide). When R¹ is aryl or heteroaryl, transition metals (e.g., palladium or copper salts or complexes) may be used to promote the arylation reaction.

Alkylation of the isoindolone (Reaction Scheme X, XXII) may be carried out by treatment of the isoindolone with a strong base (i.e. sodium bis(trimethylsilyl)amide or lithium diisopropylamide) followed by an alkyl halide (e.g. R⁸-halo) or alkyl sulfonate (e.g. R⁸-tosylate) in an inert solvent (e.g. tetrahydrofuran or dimethoxyethane). Alternatively, as seen in Scheme X, amine IVb can be treated under amide formation conditions with a ketone with the structure XB to provide a hydroxylactam XXV, which could be

subjected to reduction conditions with such reducing agents as zinc in acetic acid or triethylsilane in trifluoroacetic acid to give Ia.

Hydrazinolysis of phthalimides may be carried out by standard means known in the art. See, e.g., T. W. Greene, Protecting Groups in Organic Synthesis, Second edition, 1991.

Amide N-alkylation (Reaction Scheme VI, XXII) may be carried out by base treatment (e.g., NaH, KH, KN[Si(CH₃)₃]₂, K₂CO₃, P4-phosphazene base, or butyl lithium) in an aprotic organic solvent, followed by treatment with R⁶-halo or R⁶-O-tosylate. Use of P-phosphazene base is described in T. Pietzonka, D. Seebach, Angew. Chem. Int. Ed. Engl. **31**, 1481, 1992.

Compound III can also be prepared from compound XX as described by Cortizo, L., J. Med. Chem. **34**, 2242-2247 (1991).

Dehydration (Scheme VIII) may be carried out employing a strong acid such as hydrochloric acid, sulfuric acid or trifluoroacetic acid.

Hydrogenation (Scheme VIII) may be carried out in the presence of a conventional catalyst such as Pd/C or Pt or Rh under a H₂ atmosphere.

The addition reaction shown in Scheme IX may be carried out by treating IA¹ with an organometallic reagent XXIV, such as an organolithium or organic magnesium compound where organo is alkyl or aryl.

The deoxygenation or hydrogenation reaction (Scheme IX) is carried out in the presence of a strong acid such as trifluoroacetic acid or boron trifluoride etherate, in the presence of a hydride source such as triethyl silane or tris(trimethylsilyl)silane.

The alkylation in Schemes XII, XIII, XIV, XVI, XVIA, XVIB is carried out in the presence of

base such as butyllithium or sodium bis(trimethylsilyl)amide. It will be appreciated that R^{12} in $R^{12}Q$ may be any of the R^{12} groups as defined hereinbefore.

- 5 Alternatively, the alkylation in the above Schemes can be performed where either or both Z^1 or Z^2 is a bond, using a palladium catalyzed allylic alkylation procedure. In this reaction, the fluorenyl-type or indenyl-type precursors
- 10 (compounds XXVIII, XXXVI, XXXVII, XXXIX, XL, XLVII) are reacted with a base (sodium hydride, sodium bis(trimethylsilyl)amide or bis(trimethylsilyl)acetamide), a palladium catalyst (for example $Pd(Ph_3)_4$) and an allylic
- 15 acetate ($CH_3CO_2CH_2-CH=CH-$ or $CH_3CO_2\overset{\uparrow}{CH}-CH=CH_2$) in an inert solvent (for example THF). This reaction is to introduce either $-R^{12}$ (Scheme XII) or $-R^{11}-X^1$ (Schemes XIII, XIV, XVI, XVII) or $-R^{11}-OPG$ (Scheme XVIII, Scheme XXI). The product of this reaction
- 20 contains either an $-R^{12}$ group or an $-R^{11}-X^1$ group (or an $-R^{11}-OPG$ group) which begins with $-CH_2-CH=CH-$. Saturation of the alkene in R^{11} or R^{12} can be accomplished by standard catalytic hydrogenation conditions.

- 25 With respect to Scheme XII, the $LiAlH_4$ reduction, Swern oxidation, Wittig olefination and halogenation/sulfonation reactions are conventional reactions well known to those skilled in the art.

- 30 The sulfur oxidation in Schemes XIII, XVI and XVIII is carried out as follows.

- Sulfides of structures XXXVI, XXXVIII, XXXIX and I⁹ can be selectively oxidized to sulfoxides by 1 molar equivalent of reagents known
- 35 in the art, such as 30% H_2O_2 , $NaIO_4$, and peracids (e.g., meta-chloroperoxybenzoic acid). The resulting sulfoxides can be further transformed to

corresponding sulfones by another molar equivalent or excess of 30% H₂O₂, KMnO₄, KHSO₅, or peracids (e.g., meta-chloroperbenzoic acid). Alternatively, the sulfones can be directly prepared from

5 sulfides with 2 molar equivalents or more of oxidizing agents, such as 30% H₂O₂ and peracids (e.g., meta-chloroperbenzoic acid). In cases where an amine (such as a pyrrolidine in I⁹) is present during the oxidation, the basic nitrogen

10 may be protected by pretreatment with an acid such as HCl or CF₃CO₂H (see Scheme XIX).

To prepare examples where Z¹ or Z² is -CHOH, the compounds I and II where Z¹ or Z² is C=O can be reduced with a hydride reagent, for example NaBH₄.

15 The compounds of the invention may be employed in preventing, stabilizing or causing regression of atherosclerosis in a mammalian species by administering a therapeutically effective amount of a compound to decrease the

20 activity of MTP.

The compounds of the invention can be tested for MTP inhibitory activity employing the procedures set out in U.S. application Serial No. 117,362 filed September 3, 1993, employing MTP

25 isolated from one of the following sources:

- (1) bovine liver microsomes,
- (2) HepG₂ cells (human hepatoma cells) or
- (3) recombinant human MTP expressed in baculovirus.

30 The compounds of the invention may also be employed in lowering serum lipid levels, such as cholesterol or triglyceride (TG) levels, in a mammalian species, by administering a therapeutically effective amount of a compound to

35 decrease the activity of MTP.

The compounds of the invention may be employed in the treatment of various other

conditions or diseases using agents which decrease activity of MTP. For example, compounds of the invention decrease the amount or activity of MTP and therefore decrease serum cholesterol and TG levels, and TG, fatty acid and cholesterol absorption and thus are useful in treating hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, pancreatitis, hyperglycemia and obesity.

10 The compounds of the present invention are agents that decrease the activity of MTP and can be administered to various mammalian species, such as monkeys, dogs, cats, rats, humans, etc., in need of such treatment. These agents can be
15 administered systemically, such as orally or parenterally.

 The agents that decrease the activity or amount of MTP can be incorporated in a conventional systemic dosage form, such as a
20 tablet, capsule, elixir or injectable formulation. The above dosage forms will also include the necessary physiologically acceptable carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol),
25 anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

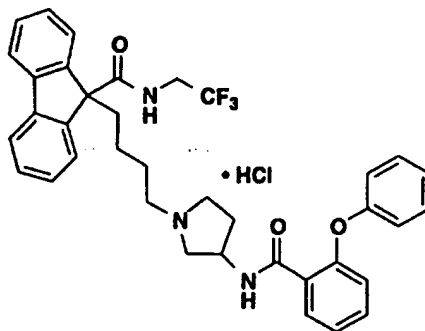
 The dose administered must be carefully
30 adjusted according to the age, weight, and condition of the patient, as well as the route of administration, dosage form and regimen, and the desired result. In general, the dosage forms described above may be administered in amounts of
35 from about 5 to about 500 mg per day in single or divided doses of one to four times daily.

The following Examples represent preferred embodiments of the invention. All temperatures are in °C unless indicated otherwise.

5

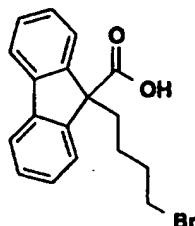
Example 1

9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride



10

A.



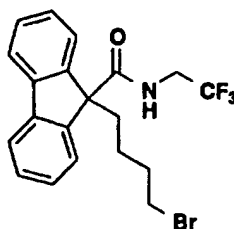
15

To a solution of 9-fluorene-9-carboxylic acid (50 g, 240 mmol) in THF (1200 mL) at 0°C was added dropwise a solution of n-butyllithium (2.5M, 211 mL, 530 mmol) in THF. The yellow reaction was stirred at 0°C for 1 h, then 1,4-dibromobutane (31.3 mL, 260 mmol) was added dropwise over 30 min. The reaction was stirred at 0°C for 30 min, then the reaction was warmed to RT for 30 h. The reaction was extracted with water (3 x 750 mL). The combined aqueous layers were extracted with ethyl ether (800 mL). The aqueous layer was made acidic with HCl solution (1N, 500 mL), then

extracted with dichloromethane (3 x 750 mL). The combined organic layers were dried over MgSO_4 . Evaporation gave title compound (71 g, 85%) as a white solid.

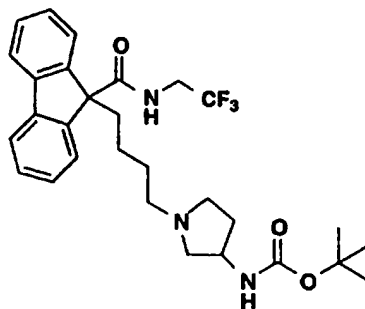
5

B.



To a solution of Part A acid (60 g, 173 mmol) and DMF (100 μL) in CH_2Cl_2 (600 mL) under argon at 0°C was added oxalyl chloride (104 mL, 2.0M in CH_2Cl_2 , 208 mmol) dropwise. The reaction was stirred at 0°C for 10 min, then warmed to RT and stirred for 1.5 h. The reaction was concentrated in vacuo to give the crude acid chloride as a yellow oil. To a suspension of 2,2,2-trifluoroethylamine hydrochloride (25.9 g, 191 mmol) in CH_2Cl_2 (500 mL) at 0°C under argon was added triethylamine (73 mL, 521 mmol) followed by dropwise addition of a solution of the crude acid chloride in CH_2Cl_2 (15 mL). The reaction was stirred at 0°C for 1 h, diluted with CH_2Cl_2 (500 mL), and washed with water (2 x 300 mL), 1N HCl (2 x 300 mL), saturated NaHCO_3 (2 x 300 mL), and brine (2 x 300 mL), then dried over MgSO_4 . Evaporation gave 80 g of a oil which was purified by flash chromatography on silica gel (2.5 kg). The crude product was loaded in a mixture of CH_2Cl_2 and hexane, and eluted with a step gradient of 10% EtOAc/hexane (4L) to 15% EtOAc/hexane (2L) to 20% EtOAc/hexane (4L). Pure fractions were combined and evaporated to give title compound (52.5 g, 71%) as a white solid (mp $88-92^\circ\text{C}$).

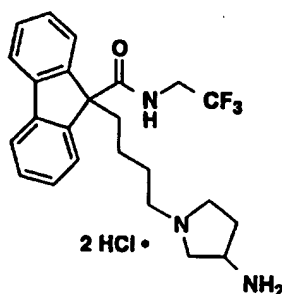
C.



- 5 A mixture of Part B compound (732 mg, 1.72 mmol), 3-(tert-butoxycarbonylamino)-pyrrolidine (383 mg, 2.06 mmol), and anhydrous potassium carbonate (356 mg, 2.58 mmol) in DMF (5 mL) was heated at 50°C under argon overnight (18 h),
- 10 cooled to RT, and the solvent removed under high vacuum. The residue was partitioned between CH₂Cl₂ (20 mL) and water (5 mL). The organic layer was washed with water (5 mL), dried over Na₂SO₄, and evaporated to give 1.2 g of an orange
- 15 solid. The crude product was purified by flash chromatography on silica gel (70 g) eluting with 5% MeOH/CH₂Cl₂ to provide title compound (673 mg, 74%) as a white foam.

20

D.



- To a solution of Part C compound (625 mg, 1.18 mmol) in dioxane (2 mL) was added 4N HCl in
- 25 dioxane (2 mL, 8 mmol). The clear solution was stirred at RT for 3 h, concentrated in vacuo, and

pumped under high vacuum overnight to give title compound (646 mg, >100%) as a white foamy solid.

E. 2-Phenoxybenzoic acid chloride

5 To a solution of 2-phenoxybenzoic acid (Aldrich) (500 mg, 2.33 mmol) and DMF (1 drop) in dichloromethane (10 mL) at RT was added dropwise a solution of oxalyl chloride in dichloromethane (2.0M, 1.28 mL, 2.56 mmol). Bubbling of escaping
10 gasses continued for 10 min after addition. The reaction was stirred at RT for 60 min, then concentrated in vacuo to give title compound as an oil.

15 F. 9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

 A solution of Part D compound (350 mg, 0.696 mmol) in CH₂Cl₂ (2 mL) was cooled to 0°C
20 under argon. Triethylamine (385 µL, 2.78 mmol) was added, which gave a cloudy mixture. A solution of Part E acid chloride in CH₂Cl₂ (1.5 mL) was added and the reaction mixture was stirred
25 at 0°C for 10 min, diluted with CH₂Cl₂ (2 mL), washed with water (2 mL) and saturated NaHCO₃ (2 mL), dried over Na₂SO₄, and then evaporated to give 450 mg of a gold-colored gum. The crude product was purified by flash chromatography on silica gel
30 (50 g) eluting with 4% MeOH/CH₂Cl₂ to provide 360 mg of the free amine as a white foam.

 To a solution of the free amine in THF (3 mL) was added 1.1N HCl in Et₂O (1.0 mL, 1.1 mmol). The reaction mixture was concentrated in vacuo,
35 and the residue was triturated with Et₂O. The resulting foam was dried in a vacuum oven (50°C,

0.2 torr) overnight to provide title compound (380 mg, 82%) as a foamy tan solid.

MS (ES, + ions) m/z 628 (M+H)

5 Anal. Calc'd for $C_{37}H_{37}F_3N_3O_3 + 0.6H_2O$:

C, 65.84; H, 5.70; N, 6.23; F, 8.44

Found: C, 66.20; H, 5.60; N, 6.13; F, 8.04.

Example 2

10 9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

To a mixture of Example 1 compound (273 mg, 0.543 mmol) and triethylamine (300 μ L, 2.17 mmol) in CH_2Cl_2 (2 mL) at 0°C under argon was added benzoyl chloride (70 μ L, 0.597 mmol). The reaction mixture was stirred at 0°C for 15 min, diluted with CH_2Cl_2 (3 mL), washed with water (1 mL) and saturated $NaHCO_3$ (2 mL), and then dried over Na_2SO_4 . Evaporation of the filtrate gave a brown foam, which was purified by flash chromatography on silica gel (60 g) eluting with 3% MeOH/ CH_2Cl_2 to provide 196 mg of product as the free amine.

A portion of the desired product (176 mg) was dissolved in MeOH (2 mL) and a solution of 1.1N HCl/ Et_2O (0.6 mL, 0.66 mmol) was added. The solution was concentrated in vacuo and the residue was triturated with Et_2O to give a foamy solid, which was pumped under high vacuum overnight to afford title compound (175 mg, 62%) as a foamy white solid.

MS (ES, + ions) m/z 536 (M+H)

Anal. Calc'd for $C_{31}H_{33}Cl_3N_3O_2 + 0.4H_2O$:

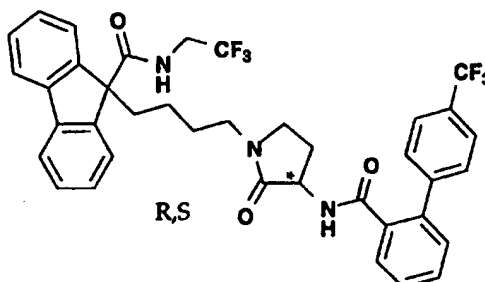
C, 64.28; H, 5.88; N, 7.25; Cl, 6.12;

F, 9.84

Found: C, 64.27; H, 5.93; N, 7.29; Cl, 5.71;

5 F, 9.73.

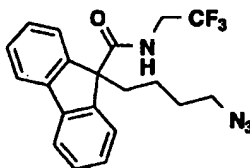
Example 3



9-[4-[2-Oxo-3-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

10

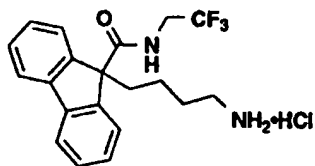
A.



A slurry of Example 1 Part B bromide (3.037 g, 7.12 mmol) and NaN_3 (2.26 g, 34.7 mmol) in DMF (15 mL) was heated at 50°C for 3 hours and then at 95°C for 2 hours. The mixture was cooled to room temperature and partitioned between EtOAc and H_2O . The organic layer was washed successively with H_2O , 1 N HCl, H_2O , and brine, then dried (Na_2SO_4), filtered and stripped to give a yellow oil which slowly solidified. Recrystallization from hexane afforded title azide compound (2.198 g) as a white solid. An additional 212 mg of material was obtained from the mother liquor to give a total of 2.41 g (87%) of title azide.

mp: 84-86°C.

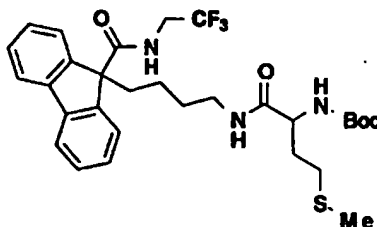
B.



A solution of Part A azide (2.253 g, 5.8 mmol) in MeOH (40 mL) was hydrogenated (balloon) over palladium (10% Pd on carbon, 250 mg) at room temperature for 1 hour. The mixture was filtered through Celite and the filtrate was stripped, re-dissolved in MeOH, and treated with 4 N HCl in dioxane. Trituration with Et₂O followed by collection of the precipitate and drying in vacuo afforded title compound (2.090 g, 90%) as a grayish white solid.
mp: 200-202°C.

15

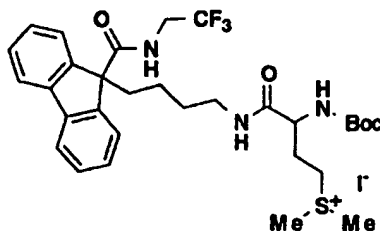
C.



A solid mixture of Part B compound (2.048 g, 5.1 mmol), N-Boc-D,L-methionine (1.280 g, 5.1 mmol), and HOBT·xH₂O (693 mg) was slurried in CH₂Cl₂ and subsequently treated with N-methylmorpholine (0.9 mL, 828 mg, 8.2 mmol) followed by ethyl-3-(3-dimethylamino)propyl carbodiimide ·HCl salt (EDAC) (1.083 g, 5.6 mmol). After stirring at room temperature for 18 hours, the homogeneous mixture was partitioned between EtOAc/Et₂O and 1 N HCl. The organic layer was washed with H₂O, 50% saturated NaHCO₃, and brine, then dried (Na₂SO₄), filtered and stripped to give racemic title compound (2.972 g, 98%) as a foam.

TLC: R_f 0.44 (6/4-EtOAc/hexanes).

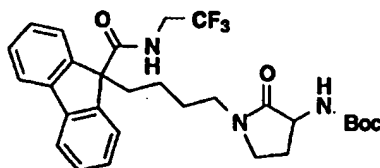
D.



5

Part C compound (2.902 g, 4.88 mmol) was dissolved in CH_3I (35 mL) and stirred at room temperature for 2 days. The solvent was stripped, then triturated and stripped from hexane twice to give crude title compound (3.74 g, 104% of theory) as a pale yellow solid which was used directly in the next reaction without further purification.

E.

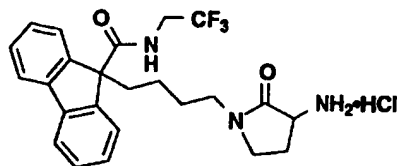


15

A solution of Part D sulfonium salt (3.069 g, 4.17 mmol) in DMF (20 mL) and CH_2Cl_2 (22 mL) at 0°C was treated all at once with solid NaH (60% in mineral oil, 400 mg, 240 mg pure, 10.0 mmol). After stirring at 0°C for 1.5 hours and at room temperature for 1.5 hours, the mixture was quenched with 0.5 N HCl and extracted with EtOAc. The EtOAc extract was washed twice with H_2O , once with saturated NaHCO_3 , and once with brine, then dried (Na_2SO_4), filtered and stripped. Flash chromatography (Merck SiO_2 , 7/3-EtOAc/hexanes) afforded title compound (1.774 g, 78%) as a white foam.

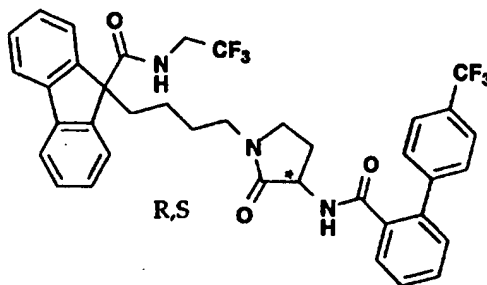
TLC: R_f 0.21 (6/4-EtOAc/hexane).

F.



A solution of Part E compound (1.752 g, 3.2 mmol) in 1,4-dioxane (8 mL) was treated with 4 N HCl in 1,4-dioxane (5 mL). After 5 hours, the solvent was stripped and the residue was azeotroped twice from CH₂Cl₂/Et₂O and triturated from Et₂O/hexane. The solid was collected by filtration and dried in vacuo to give title compound (1.576 g, 102% of theory) as a white solid.

G.



15

A solid mixture of Part F compound (250 mg, 0.52 mmol), 4'-(trifluoromethyl)-2-biphenylcarboxylic acid (145 mg, 0.54 mmol), and HOBT·xH₂O (70 mg) was slurried in CH₂Cl₂ (5 mL) and subsequently treated with N-methyl morpholine (86 uL, 79 mg, 0.78 mmol) followed by EDAC (111 mg, 0.58 mmol). After stirring at room temperature for 18 hours, the mixture was partitioned between EtOAc and 1 N HCl. The EtOAc extract was washed successively with H₂O, saturated NaHCO₃ and brine, then dried (Na₂SO₄), filtered and stripped. Flash chromatography (Merck SiO₂, 8/2-EtOAc/hexanes) afforded title compound (310 mg, 86%) as a white foam.

TLC: R_f 0.21 (8/2-EtOAc/hexanes)

MS: $(M+H)^+$ @ 694; $(M-H)^-$ 692; $(M+NH_4)^+$ 711

HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted
5 with 0% to 100% B, 30 minute gradient, (A = 90%
H₂O-10% MeOH-0.2% H₃PO₄ and B = 10% H₂O-90% MeOH-
0.2% H₃PO₄) flow rate at 1.5 ml/min detecting at
220 nm; t_R = 30.98 min (98.1%).

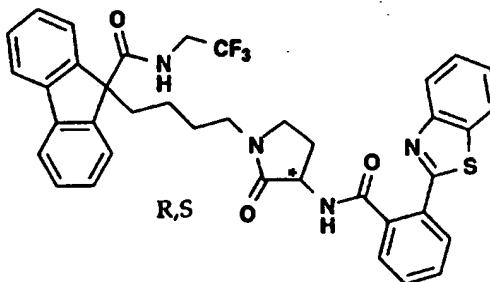
Microanalysis Calc'd for C₃₈H₃₃F₆N₃O₃ + 0.13CH₂Cl₂:

10 C, 64.96; H, 4.76; N, 5.96; F, 16.17;
Cl, 1.35

Found: C, 64.86; H, 4.80; N, 5.89; F, 16.22;
Cl 1.34.

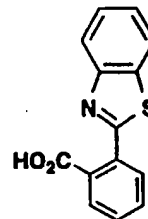
15

Example 4



9-[4-{3-[[2-(2-Benzothiazolyl)benzoyl]amino]-2-oxo-1-pyrrolidiny]butyl]-
N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

A slurry of Example 3 Part F amine



20 hydrochloride (200 mg, 0.415 mmol), (98
mg, 0.38 mmol), and HOBT·xH₂O (56 mg) in CH₂Cl₂ (5
mL) was treated successively with N-methyl
morpholine (70 μ L, 65 mg, 0.65 mmol) and EDAC (89
mg, 0.46 mmol) at room temperature. After 18
25 hours, the mixture was partitioned between EtOAc
and saturated NaHCO₃. The EtOAc extract was washed
successively with H₂O, 1 N HCl, and brine, then

dried (Na_2SO_4), filtered, and stripped repeatedly from CH_2Cl_2 to give title compound (249 mg, 95%) as a white foam.

TLC: R_f 0.19 (EtOAc)

5 MS: $(M+H)^+$ @ 683; $(M-H)^-$ 681

HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted with 40% to 100% B, 20 minute gradient, (A = 90% H_2O -10% MeOH -0.2% H_3PO_4 and B = 10% H_2O -90% MeOH -0.2% H_3PO_4) flow rate at 1.5 ml/min detecting at

10 254 nm; t_R = 18.9 min (96.6%).

Microanalysis Calc'd for $\text{C}_{38}\text{H}_{33}\text{F}_3\text{N}_4\text{O}_3\text{S}+0.09 \text{CH}_2\text{Cl}_2$:

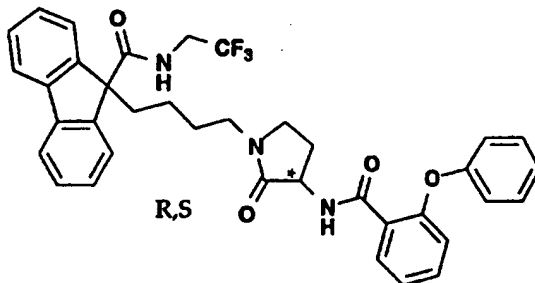
C, 66.27; H, 4.84; N, 8.12; F, 8.26;

S, 4.64; Cl, 0.92

Found: C, 65.92; H, 3.92; N, 7.81; F, 7.98;

15 S, 4.56; Cl, 0.70.

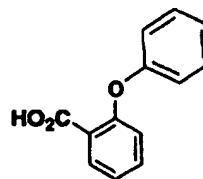
Example 5



9-[4-[2-Oxo-3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

20

A slurry of Example 3 Part F amine



hydrochloride (200 mg, 0.415 mmol),
(85 mg, 0.40 mmol), and HOBT·xH₂O (56 mg) in CH_2Cl_2
(7 mL) was treated successively with N-methyl
25 morpholine (70 μL , 65 mg, 0.65 mmol) and EDAC (89
mg, 0.46 mmol) at room temperature. After 22
hours, the mixture was partitioned between EtOAc
and saturated NaHCO_3 . The EtOAc extract was washed

successively with H₂O, 1 N HCl, and brine, then dried (Na₂SO₄), filtered, and stripped repeatedly from CH₂Cl₂ to give title compound (224 mg, 87%) as a white foam.

5

TLC: R_f 0.46 (EtOAc)

MS: (M+H)⁺ @ 642; (M-H)⁻ 640

HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted with 40% to 100% B, 20 minute gradient, (A = 90% H₂O-10% MeOH-0.2% H₃PO₄ and B = 10% H₂O-90% MeOH-0.2% H₃PO₄) flow rate at 1.5 ml/min detecting at 254 nm; t_R = 19.7 min (100%).

10

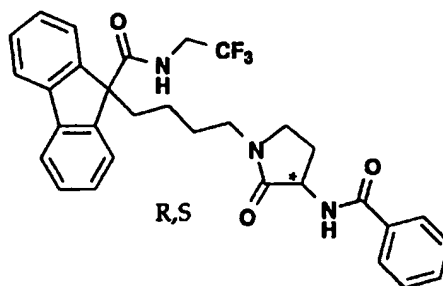
Microanalysis Calc'd for C₃₇H₃₄F₃N₃O₄:

C, 69.26; H, 5.34; N, 6.55; F, 8.88

15

Found: C, 68.92; H, 5.25; N, 6.42; F, 8.70.

Example 6



9-[4-[3-(Benzoylamino)-2-oxo-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

20

A solution of Example 3 Part F amine hydrochloride (200 mg, 0.415 mmol) and triethylamine (TEA) (200 μ L, 145 mg, 1.43 mmol) in CH₂Cl₂ (4 mL) at 0°C was treated with benzoyl chloride (48 μ L, 58 mg, 0.41 mmol). After 45 minutes, the mixture was quenched with saturated NaHCO₃ and extracted with EtOAc. The EtOAc extract was washed successively with H₂O, 1 N HCl, H₂O, and brine, then dried (Na₂SO₄), filtered and stripped to give title compound (231 mg, 98%) as a white foam.

30

TLC: R_f 0.35 (EtOAc)

MS: $(M+H)^+$ @ 550; $(M-H)^-$ 548

HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted with 40% to 100% B, 20 minute gradient, (A = 90%

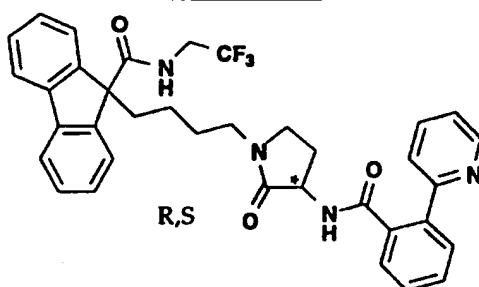
5 H₂O-10% MeOH-0.2% H₃PO₄ and B = 10% H₂O-90% MeOH-0.2% H₃PO₄) flow rate at 1.5 ml/min detecting at 254 nm; t_R = 16.2 min (96.7%).

Microanalysis Calc'd for C₃₁H₃₀F₃N₃O₃ + 0.2EtOAc:

C, 67.34; H, 5.62; N, 7.41; F, 9.59

10 Found: C, 67.15; H, 5.55; N, 7.13; F, 9.73.

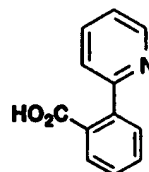
Example 7



9-[4-[2-Oxo-3-[[2-(2-pyridinyl)benzoyl]amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

15

A slurry of Example 3 Part F amine



hydrochloride (202 mg, 0.419 mmol), (88 mg, 0.44 mmol), and 1-hydroxy-7-azabenzotriazole (HOAT) (55 mg) in CH₂Cl₂ (3 mL) was treated

20 successively with N-methyl morpholine (56 μ L, 52 mg, 0.51 mmol) and EDAC (87.5 mg, 0.46 mmol) at room temperature. After 18 hours, the mixture was partitioned between EtOAc and saturated NaHCO₃. The EtOAc extract was washed successively with H₂O

25 and brine, then dried (Na₂SO₄), filtered, and stripped. The residue was flash chromatographed (Merck SiO₂, 5/95-MeOH/CH₂Cl₂ as eluant) to give title compound (259 mg, 94%) as a white foam.

TLC: R_f 0.47 (1/9-MeOH/CH₂Cl₂)

MS: (M+H)⁺ @ 627

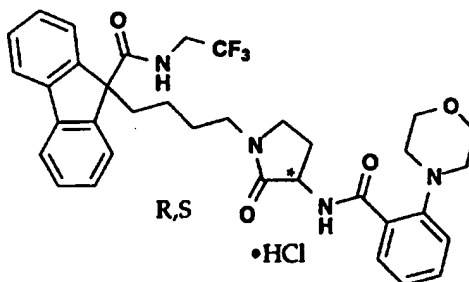
HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted
5 with 40% to 100% B, 20 minute gradient, (A = 90%
H₂O-10% MeOH-0.2% H₃PO₄ and B = 10% H₂O-90% MeOH-
0.2% H₃PO₄) flow rate at 1.5 ml/min detecting at
254 nm; t_R = 11.6 min (98.9%).

Microanalysis Calc'd for C₃₆H₃₃F₃N₄O₃+0.35 CH₂Cl₂:

10 C, 66.51; H, 5.18; N, 8.54; F, 8.68

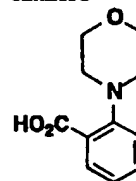
Found: C, 66.88; H, 5.07; N, 8.36; F, 7.91.

Example 8



15 9-[4-{3-[[2-(4-Morpholinyl)benzoyl]amino]-2-oxo-1-pyrrolidinyl]butyl]-
N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

A slurry of Example 3 Part F amine



hydrochloride (200 mg, 0.415 mmol), (111
mg, 0.53 mmol), and HOAT (53 mg) in CH₂Cl₂ (5 mL)
20 was treated successively with N-methyl morpholine
(100 μ L, 93 mg, 0.91 mmol) and EDAC (90 mg, 0.47
mmol) at room temperature. After 20 hours, the
mixture was partitioned between EtOAc and
saturated NaHCO₃. The EtOAc extract was washed
25 successively with H₂O and brine, then dried
(Na₂SO₄), filtered, and stripped to give an oil.
The residue was flash chromatographed (Merck SiO₂,
5/95-MeOH/CH₂Cl₂ as eluant) to give the free base

of title compound (141 mg, 53%) as pale yellow oil. The oil was dissolved in 1,4-dioxane (2 mL), treated with 4 N HCl in 1,4-dioxane (150 μ L) and added via cannula to rapidly swirling Et₂O (30 mL).

- 5 The precipitate was collected by filtration and dried in vacuo to give title compound (101 mg, 35% from Example 3 Part F compound) as a pink solid.

TLC: R_f 0.64 (1/9-MeOH/CH₂Cl₂)

- 10 MS: (M+H)⁺ @ 635

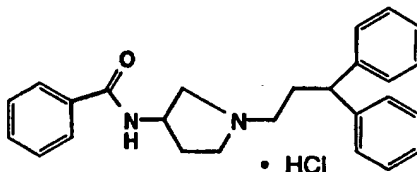
HPLC: YMC S3 ODS column (6.0 x 150 mm); Eluted with 40% to 100% B, 20 minute gradient, (A = 90% H₂O-10% MeOH-0.2% H₃PO₄ and B = 10% H₂O-90% MeOH-0.2% H₃PO₄) flow rate at 1.5 ml/min detecting at

- 15 254 nm; t_R = 16.9 min (98.7%).

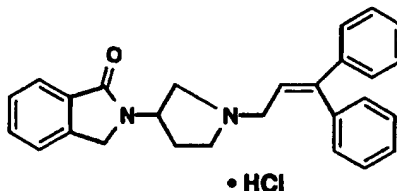
The following Examples represent preferred embodiments of the invention and may be prepared employing procedures described herein.

20

Example 8A

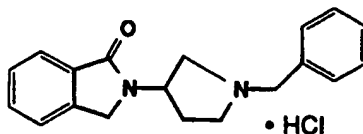


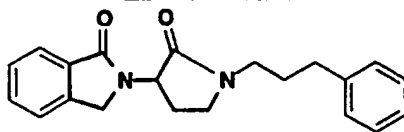
Example 8B



25

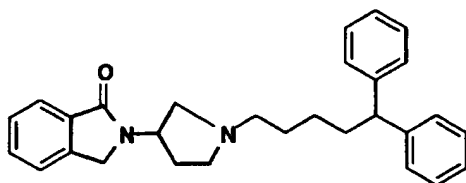
Example 8C



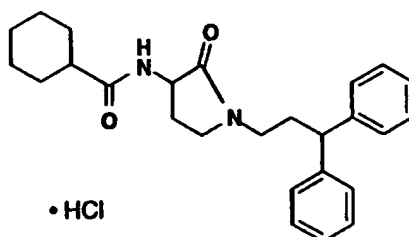
Example 8D

• HCl

5

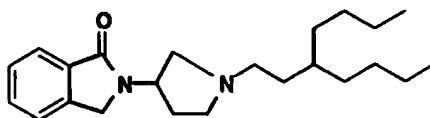
Example 8E

• HCl

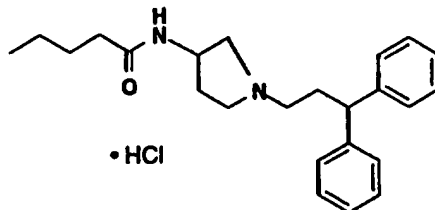
Example 8F

• HCl

10

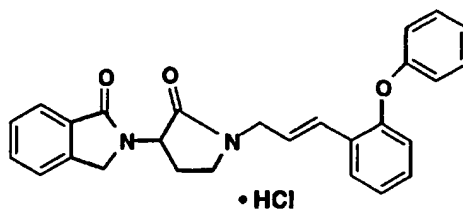
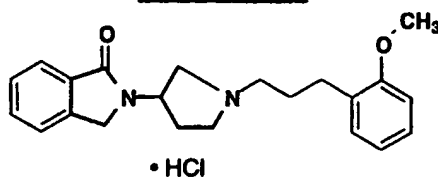
Example 9

• HCl

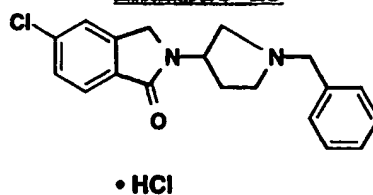
Example 10

• HCl

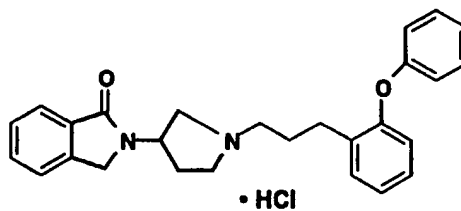
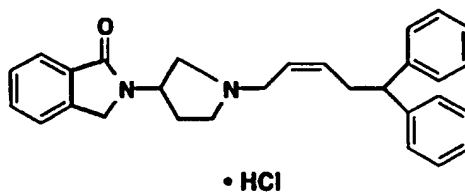
15

Example 11Example 12

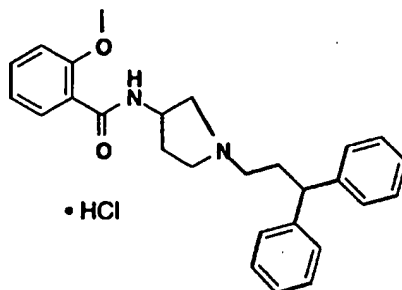
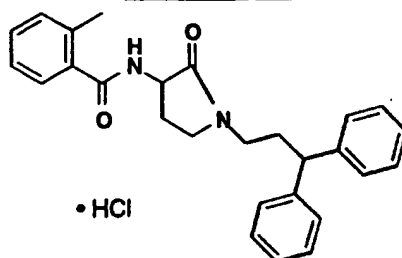
5

Example 13

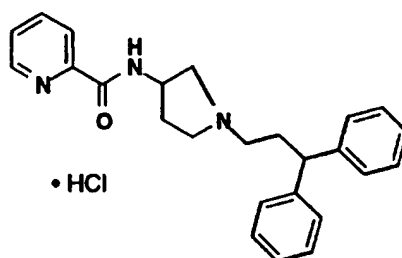
10

Example 14Example 15

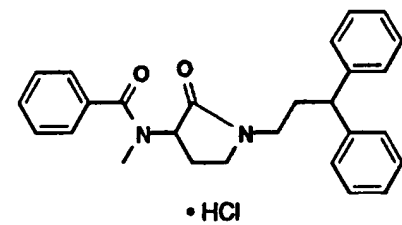
15

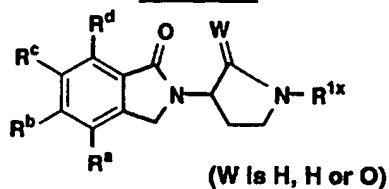
Example 16Example 17

5

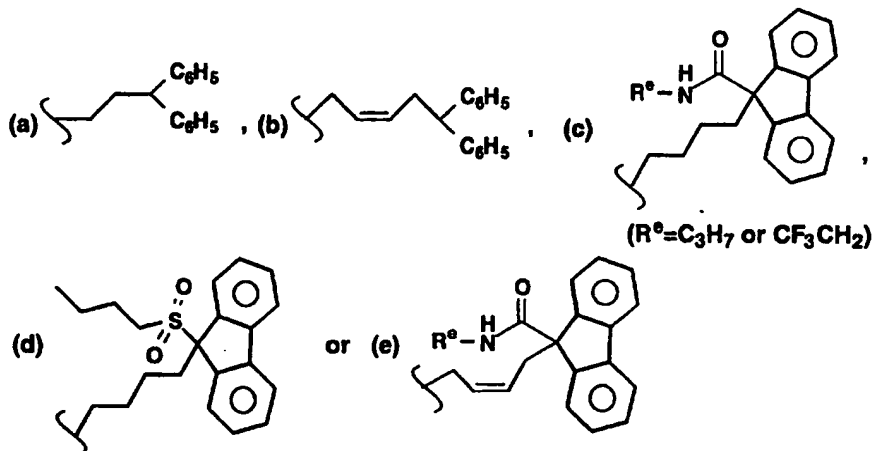
Example 18

10

Example 19

Examples 20 to 202Table A

where R^{1x} is

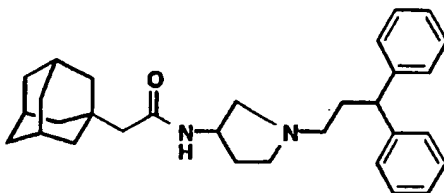
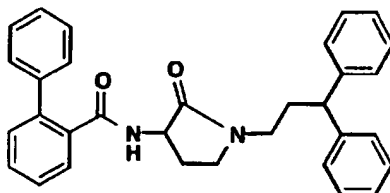


5

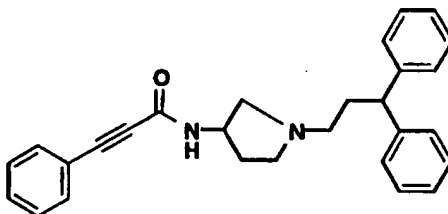
	R ^a	R ^b	R ^c	R ^d
10	H	H	H	F
	H	H	H	
	H	H	H	
15	H	H	F	Cl
	H	H	CF ₃	H
	H	OCH ₃	H	H
	H	H	H	
20	H	H	H	H
	F	Cl	H	H
	H	H		H
	H	H	H	
	H	H	H	

Table A (continued)

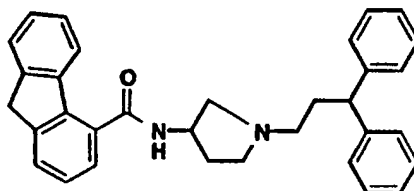
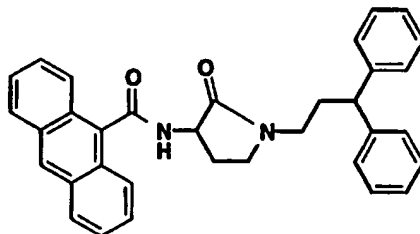
	R^a	R^b	R^c	R^d
5		H	H	
	H	H	H	H
	H	H	Cl	
	H	H	H	H
	H	H	H	H
10	H	H	H	Cl
	H	H	CH ₃	H
	H	CH ₃	H	
	SCH ₃	H	H	H
	H	H	OCH ₃	H
15	H	H	H	SCH ₃
	H	H	H	H
	H	H	H	
	H		H	H
	H	H	H	
20	H	H	H	

Example 203Example 204

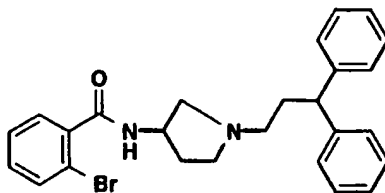
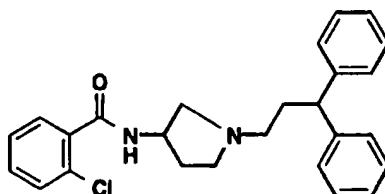
5

Example 205

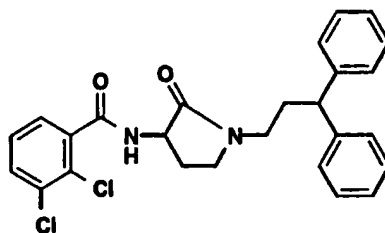
10

Example 206Example 207

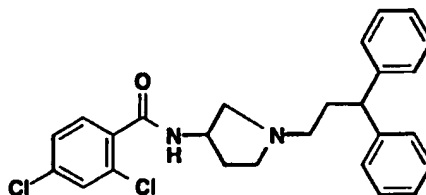
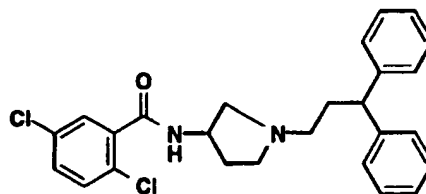
15

Example 208Example 209

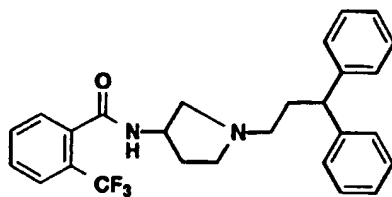
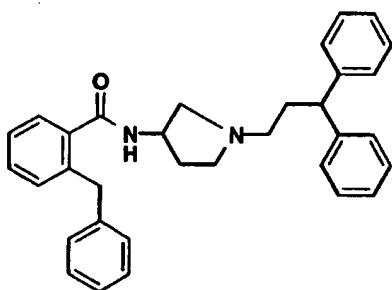
5

Example 210

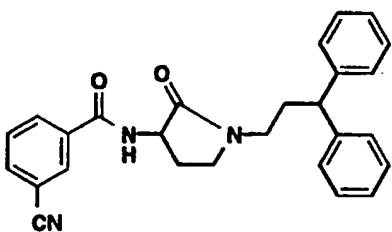
10

Example 211Example 212

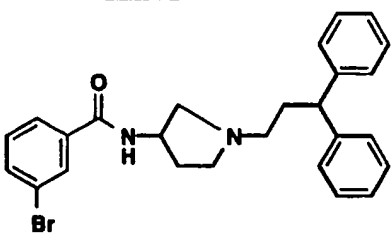
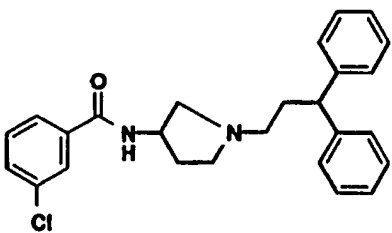
15

Example 213Example 214

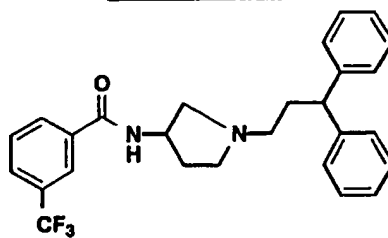
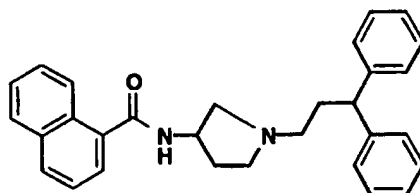
5

Example 215

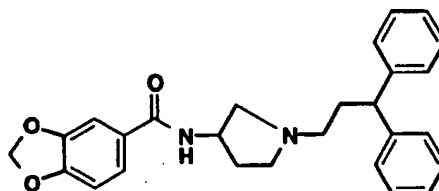
10

Example 216Example 217

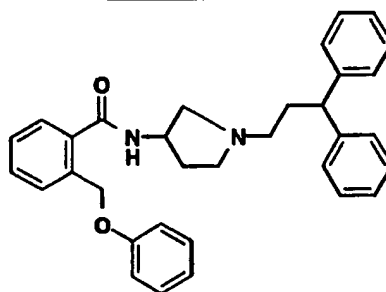
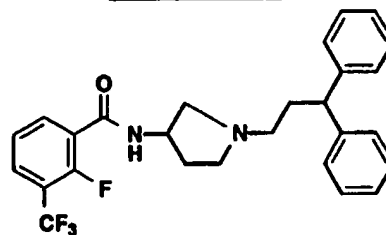
15

Example 218Example 219

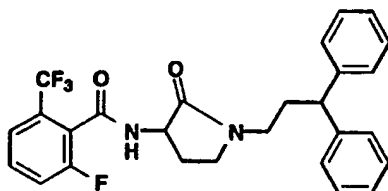
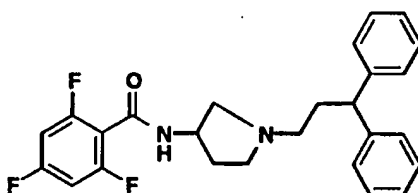
5

Example 220

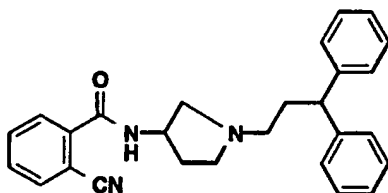
10

Example 221Example 222

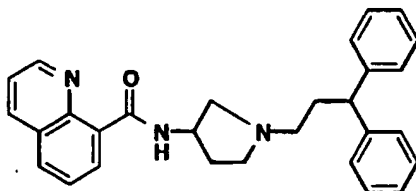
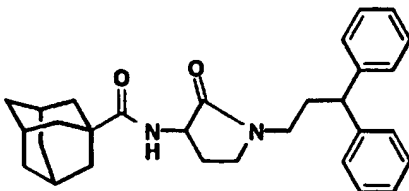
15

Example 223Example 224

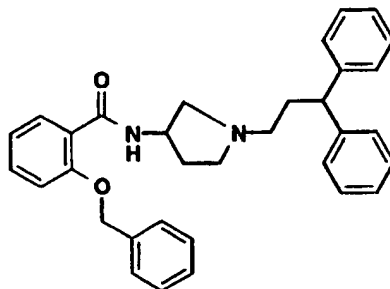
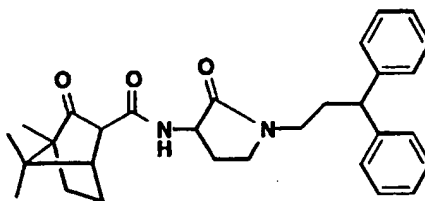
5

Example 225

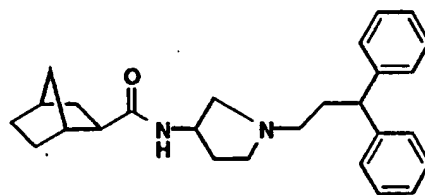
10

Example 226Example 227

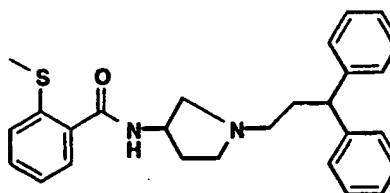
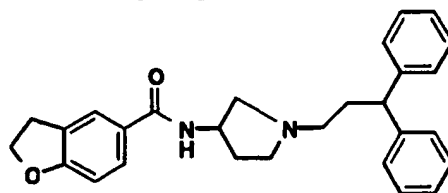
15

Example 228Example 229

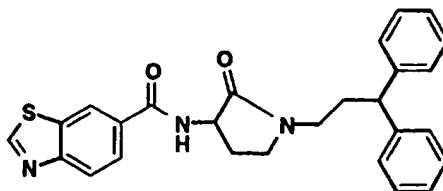
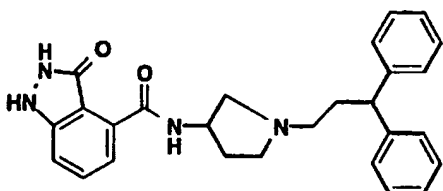
5

Example 230

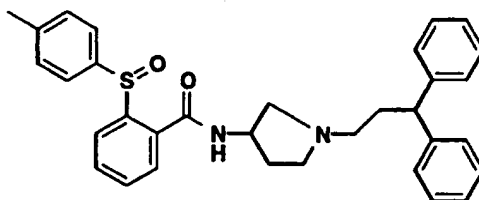
10

Example 231Example 232

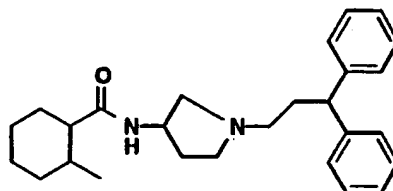
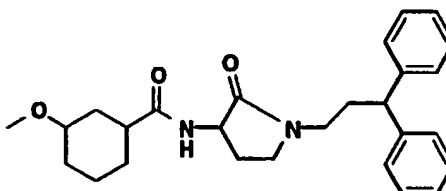
15

Example 233Example 234

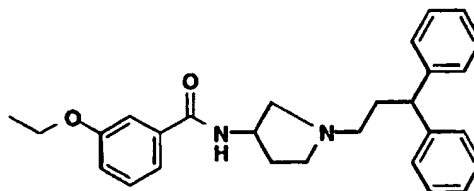
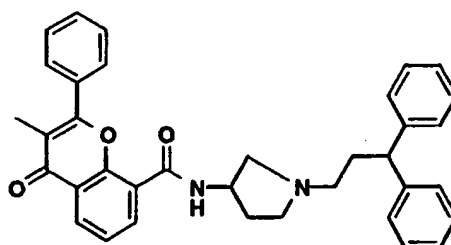
5

Example 235

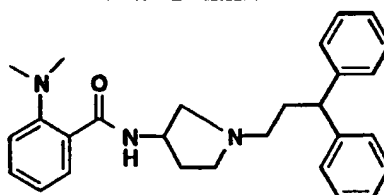
10

Example 236Example 237

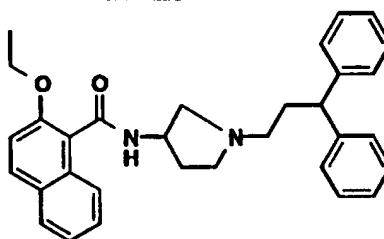
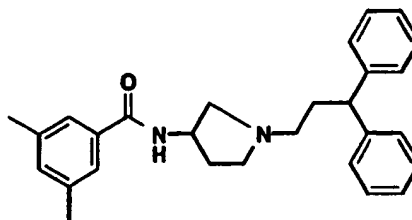
15

Example 238Example 239

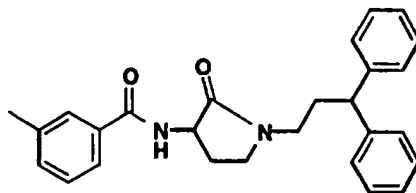
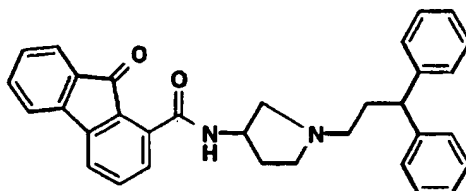
5

Example 240

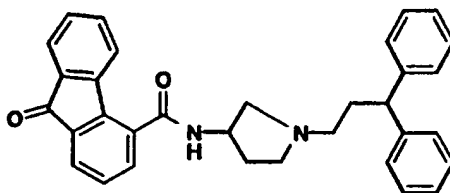
10

Example 241Example 242

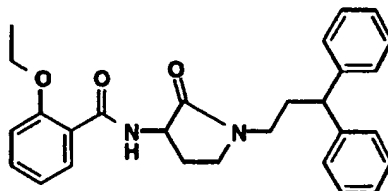
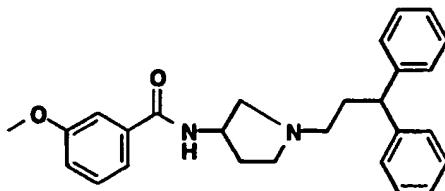
15

Example 243Example 244

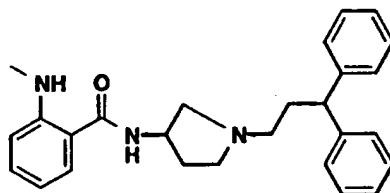
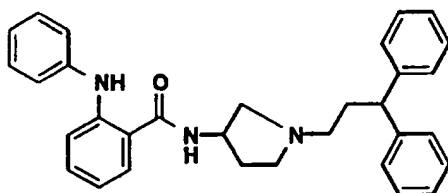
5

Example 245

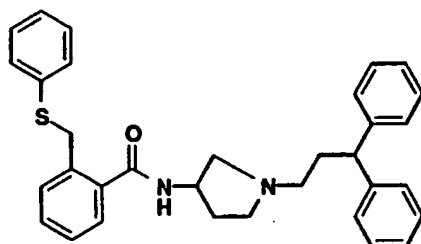
10

Example 246Example 247

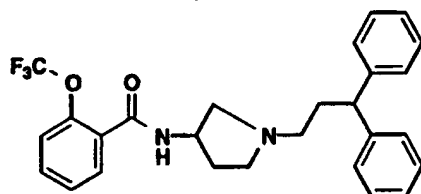
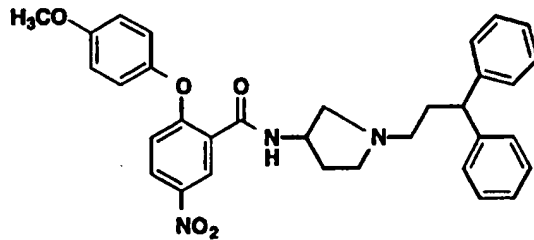
15

Example 248Example 249

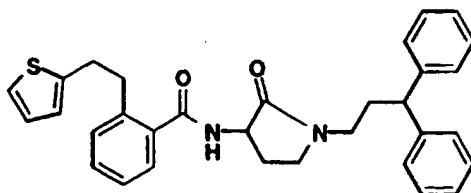
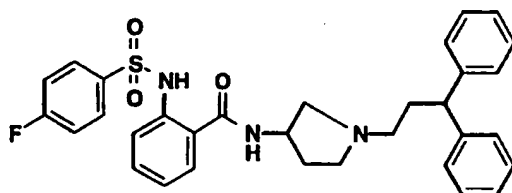
5

Example 250

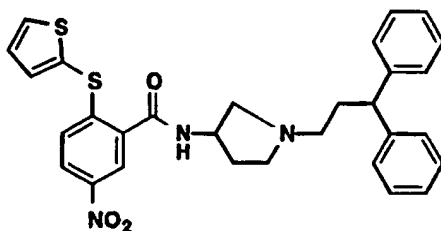
10

Example 251Example 252

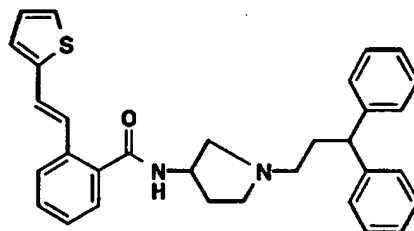
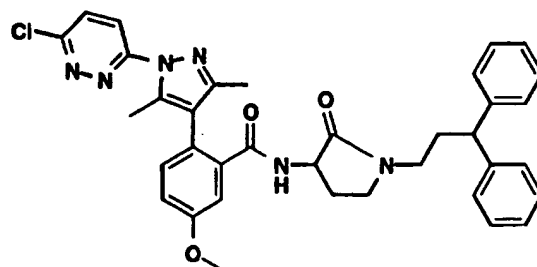
15

Example 253Example 254

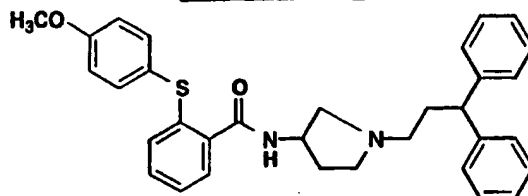
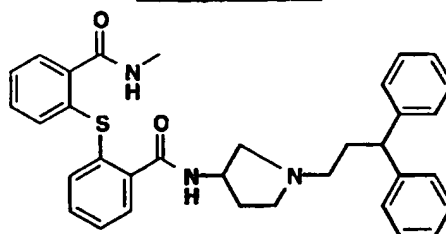
5

Example 255

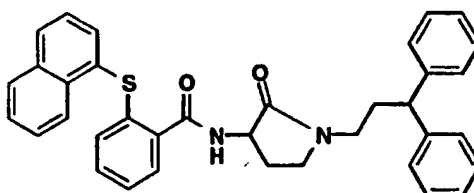
10

Example 256Example 257

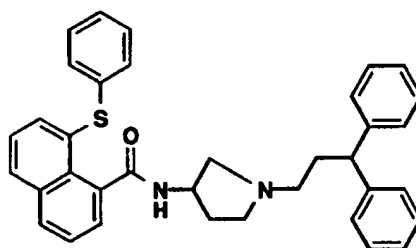
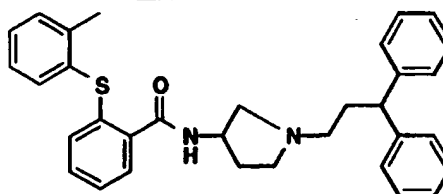
15

Example 258Example 259

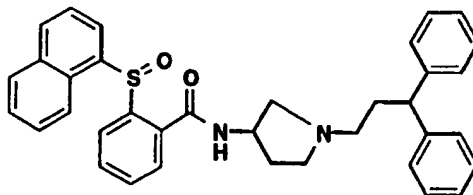
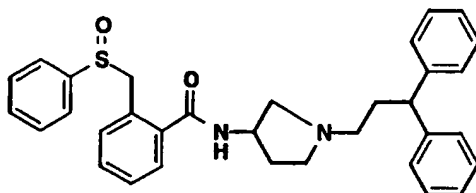
5

Example 260

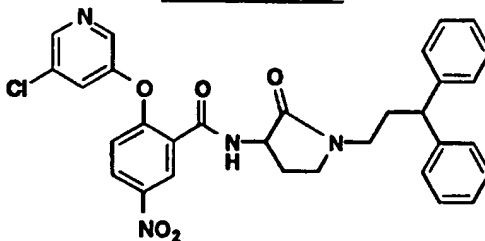
10

Example 261Example 262

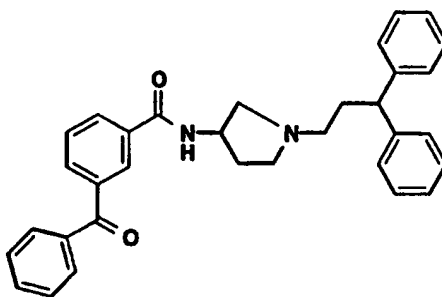
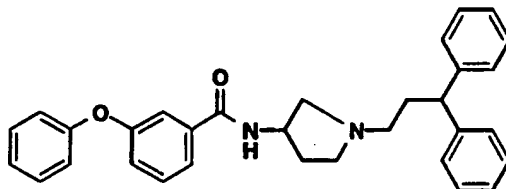
15

Example 263Example 264

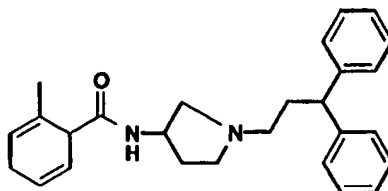
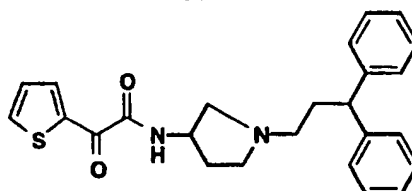
5

Example 265

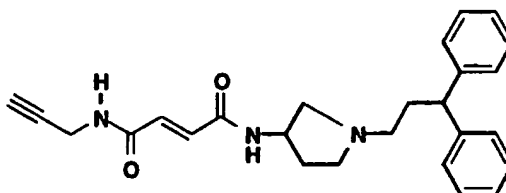
10

Example 266Example 267

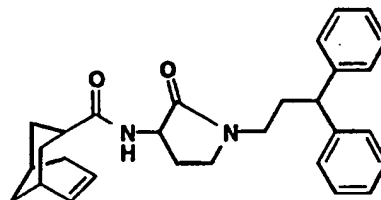
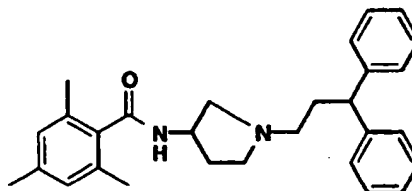
15

Example 268Example 269

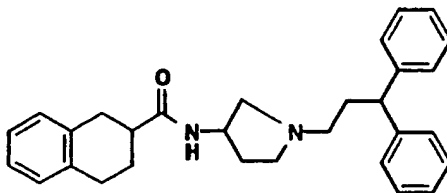
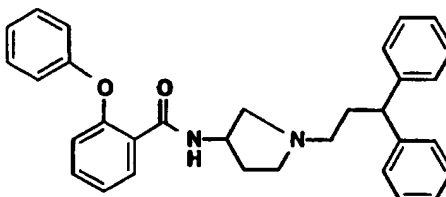
5

Example 270

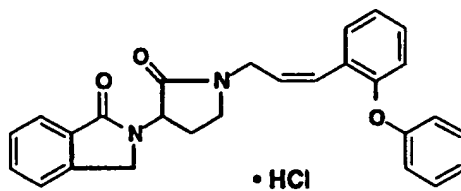
10

Example 271Example 272

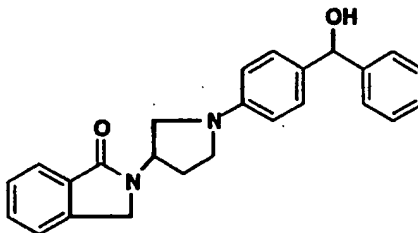
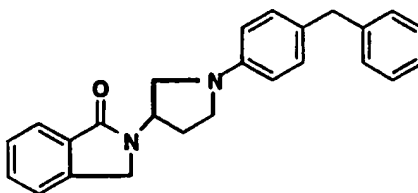
15

Example 273Example 274

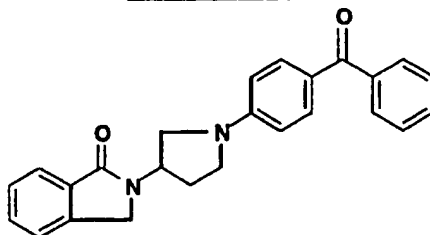
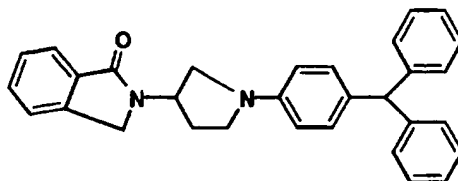
5

Example 275

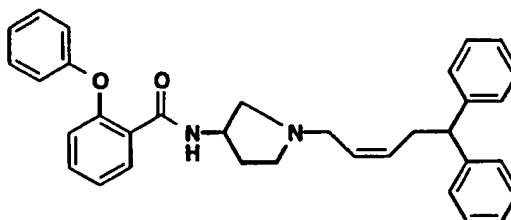
10

Example 276Example 277

15

Example 278Example 279

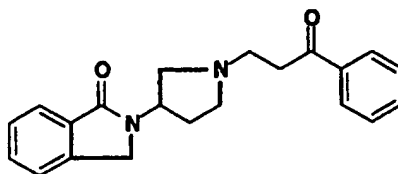
5

Example 280

10

Example 281

(Z)-N-[1-(5,5-Diphenyl-2-pentenyl)-3-pyrrolidinyl]-2-phenoxybenzamide

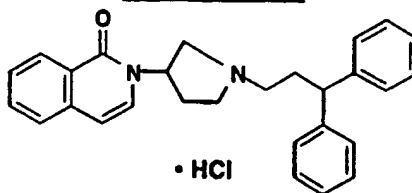
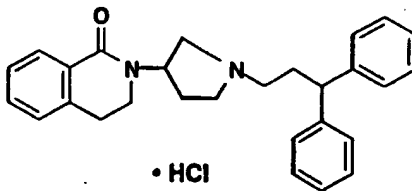
Example 282

15

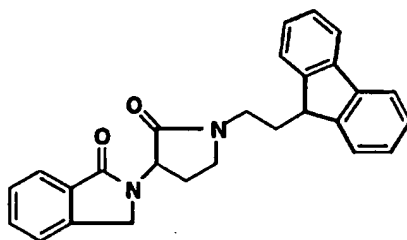
Example 283

2,3-Dihydro-2-[1-[3-phenyl-3-(4-propylphenyl)-
propyl]-3-pyrrolidinyl]-1H-isoindol-1-one,
monohydrochloride

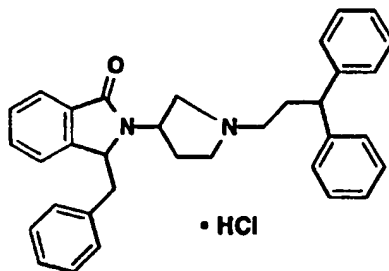
5

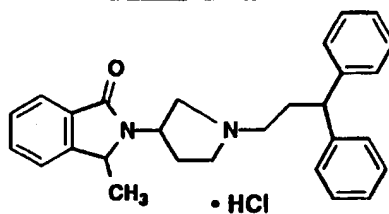
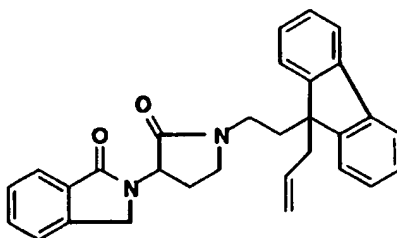
Example 284**Example 285**

10

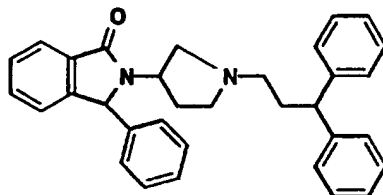
Example 286

15

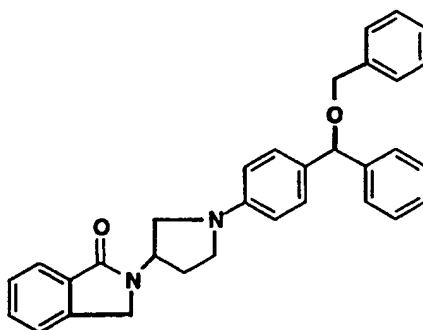
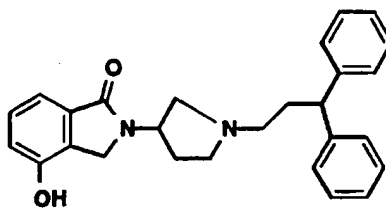
Example 287

Example 288Example 289

5

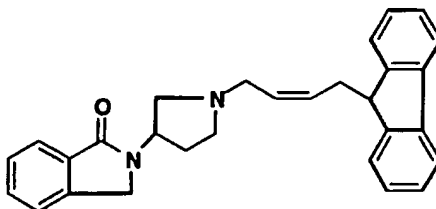
Example 290

10

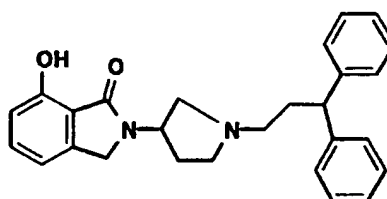
Example 291Example 292

15

Example 293

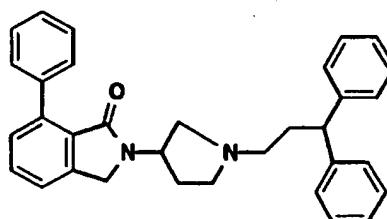


Example 294



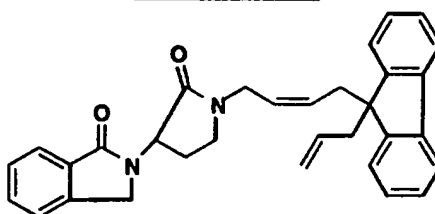
5

Example 295

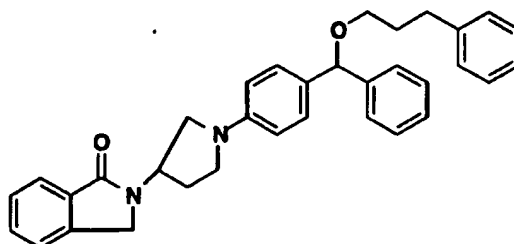


10

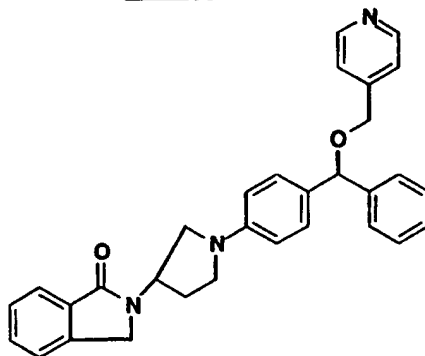
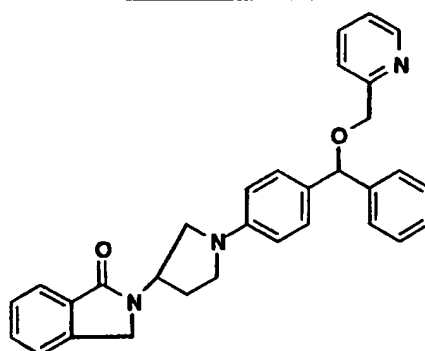
Example 296



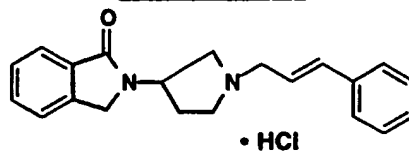
Example 297



15

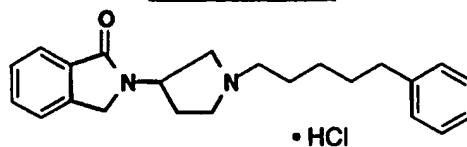
Example 298Example 299

5

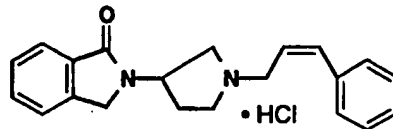
Example 300

• HCl

10

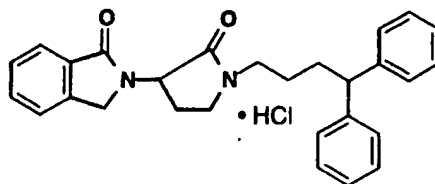
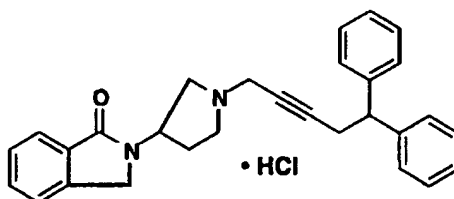
Example 301

• HCl

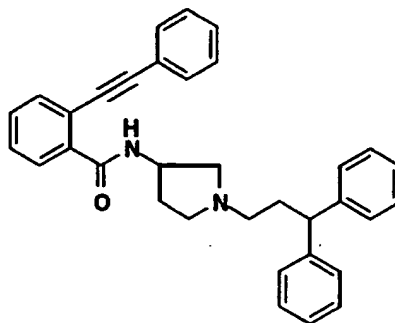
Example 302

• HCl

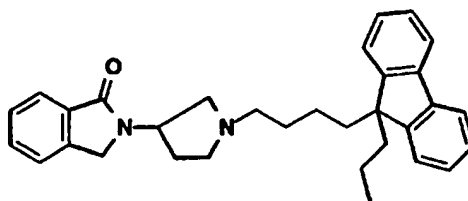
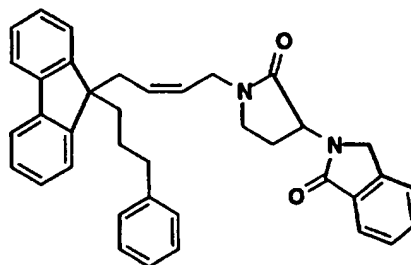
15

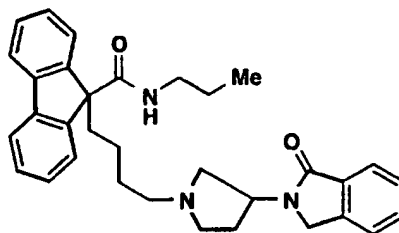
Example 303Example 304

5

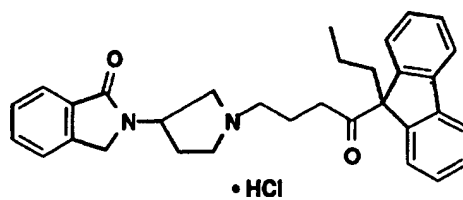
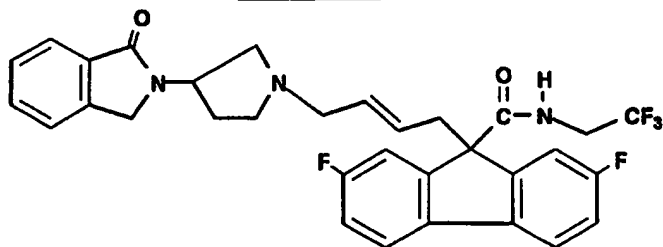
Example 305

10

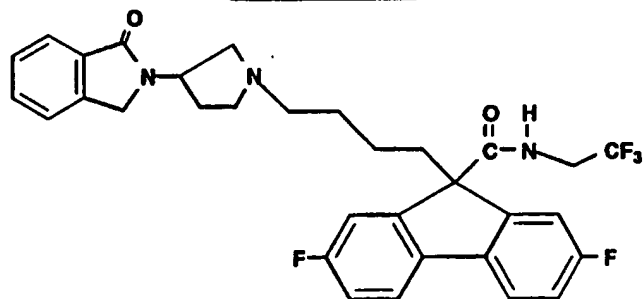
Example 306Example 307

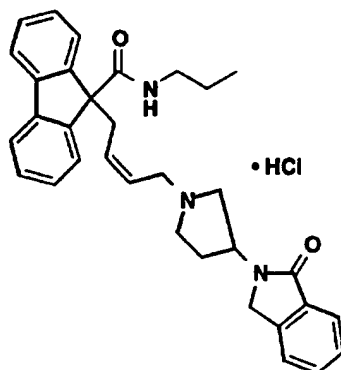
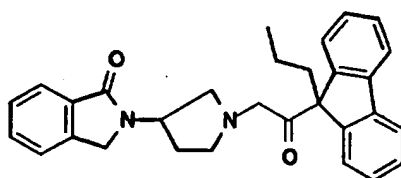
Example 308

5

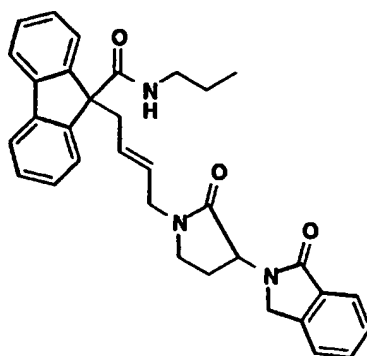
Example 309**Example 310**

10

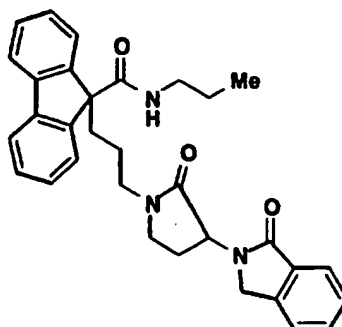
Example 311

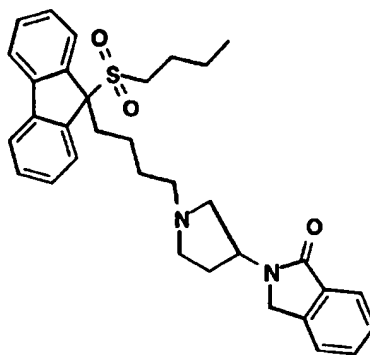
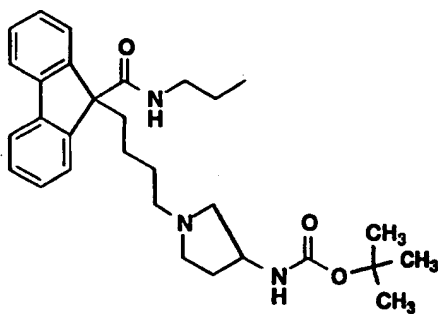
Example 312Example 313

5

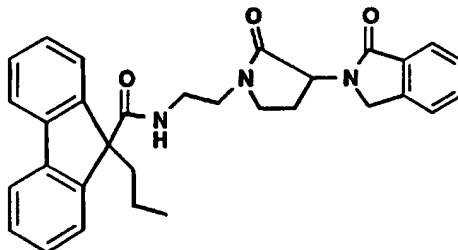
Example 314

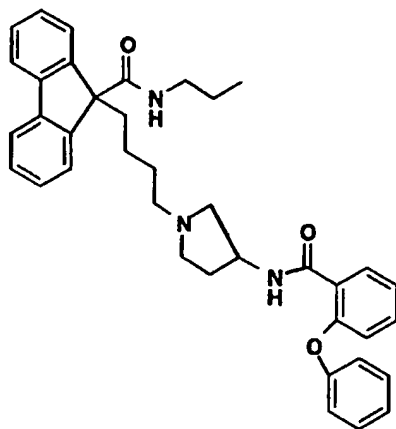
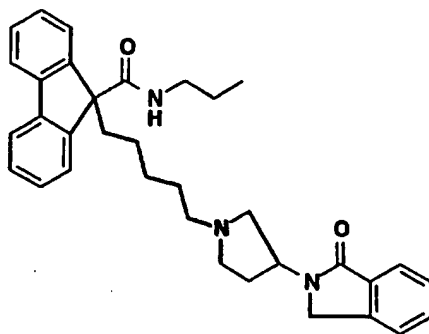
10

Example 315

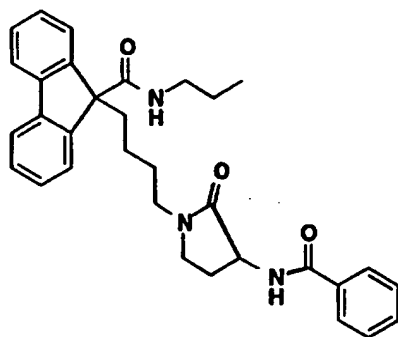
Example 316Example 317

5

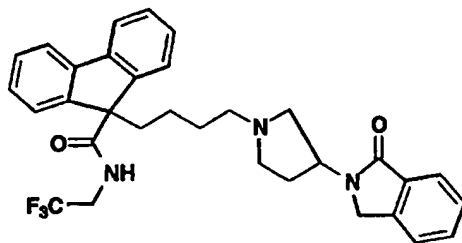
Example 318

Example 319Example 320

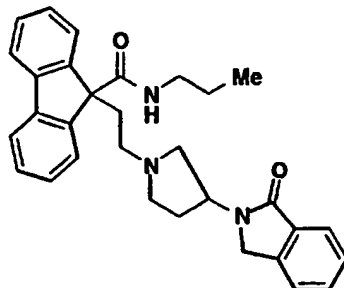
5

Example 321

Example 322

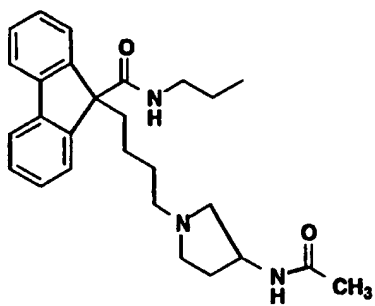


Example 323



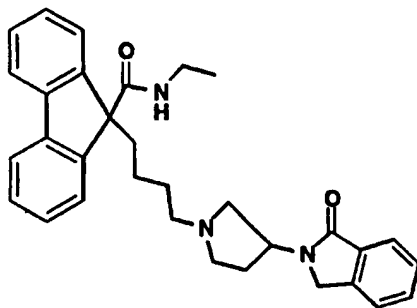
5

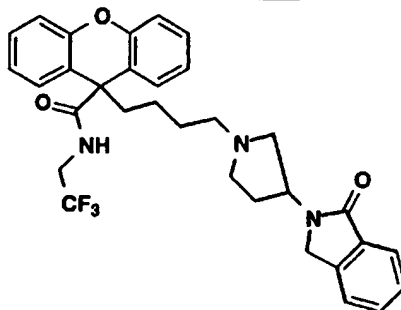
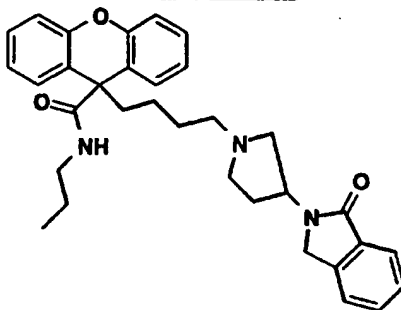
Example 324



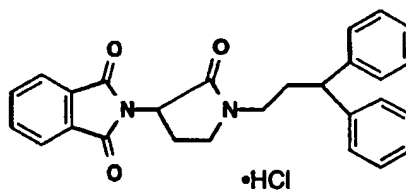
10

Example 325

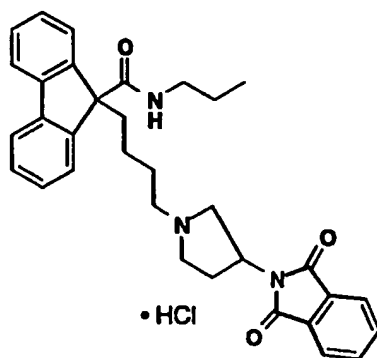


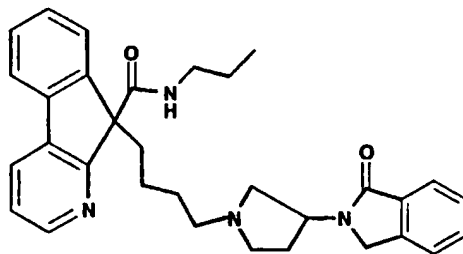
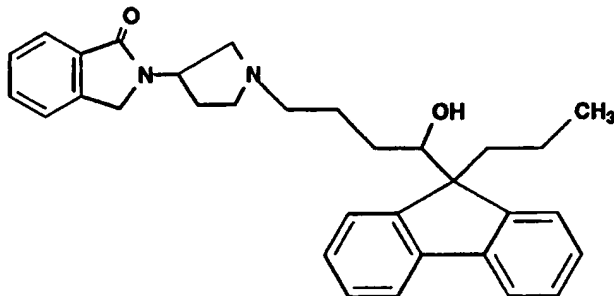
Example 326Example 327

5

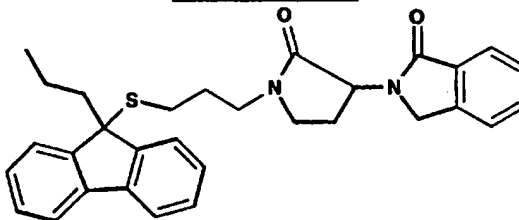
Example 328

10

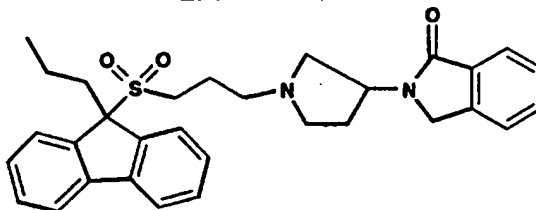
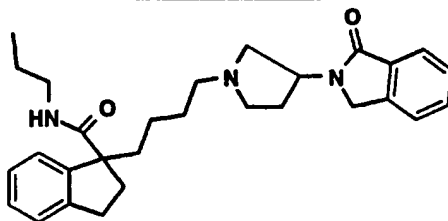
Example 329

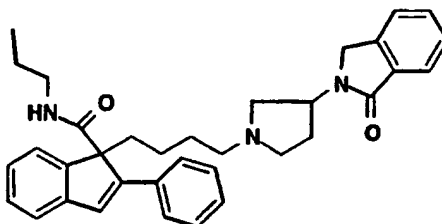
Example 330Example 331

5

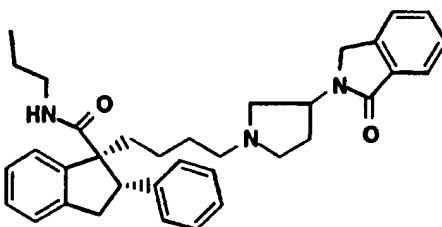
Example 332

10

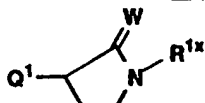
Example 333Example 334

Example 335

5

Example 336

Additional compounds falling within the scope of the present invention are described by the following structures. Substituents for each example are identified in the table following each structure.

Table B

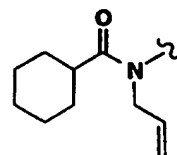
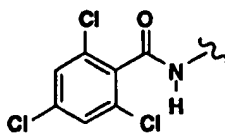
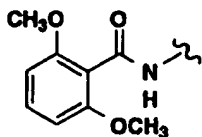
(Where W is H, H or O)

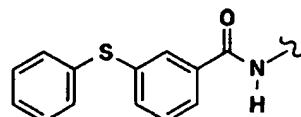
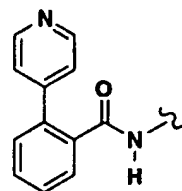
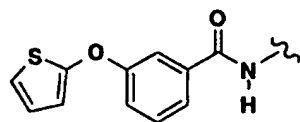
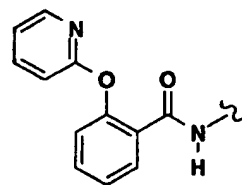
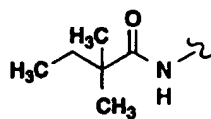
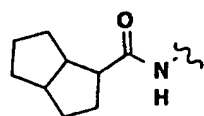
15

where R^{1x} is (a), (b), (c), (d) or (e) as in Table A

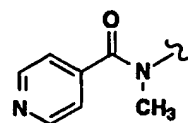
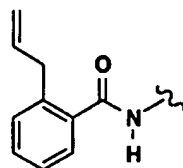
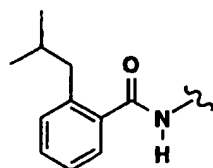
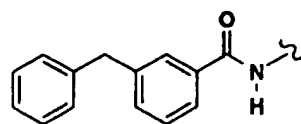
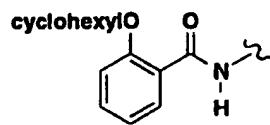
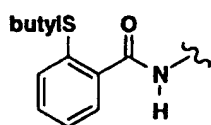
Examples of Q^1

20





5



10

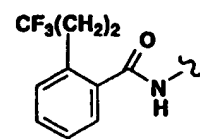
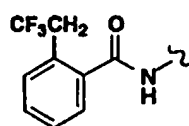
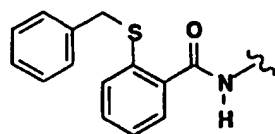
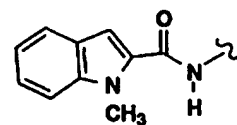
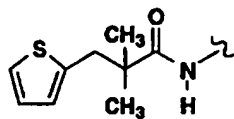
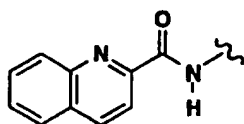
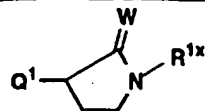
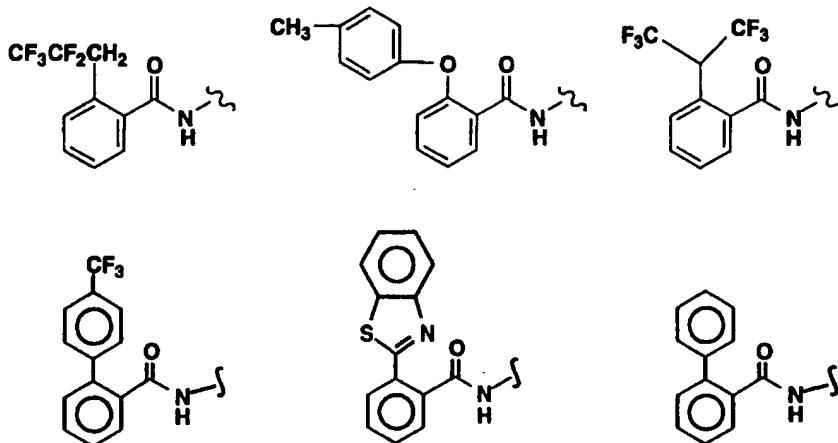


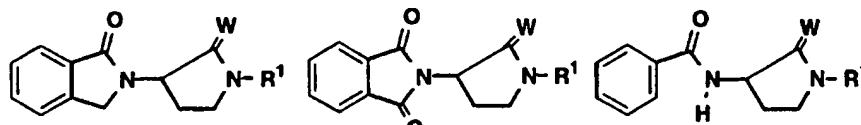
Table B (continued)

Examples of Q¹

5

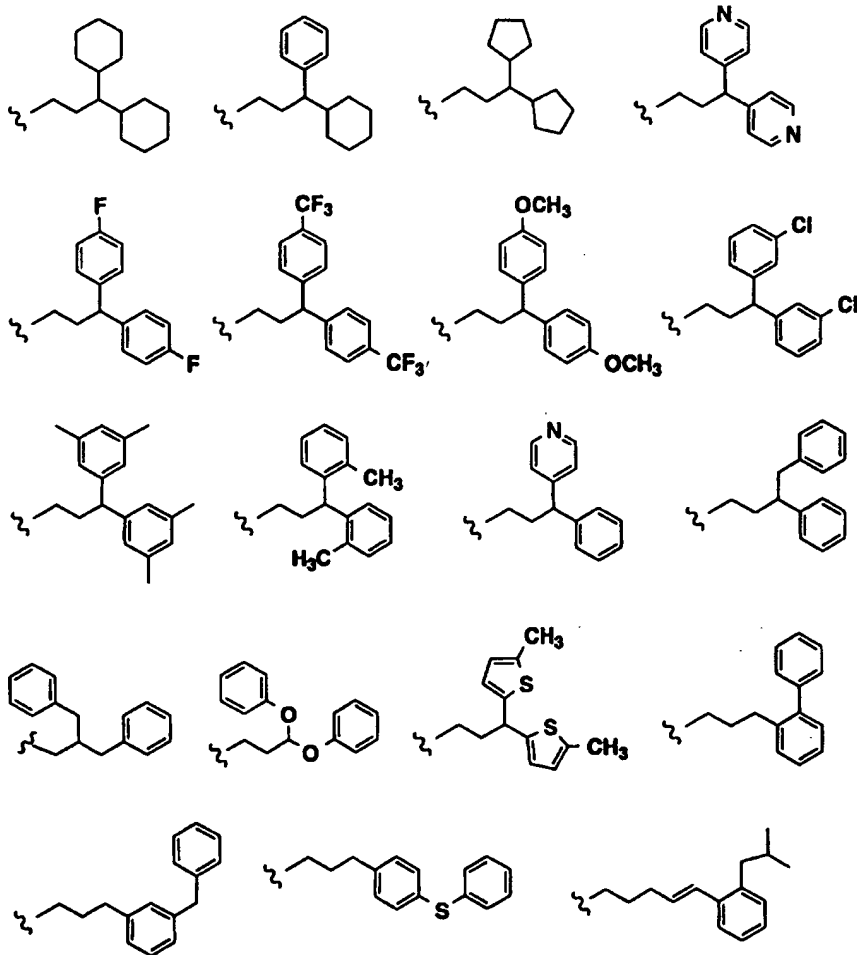


10

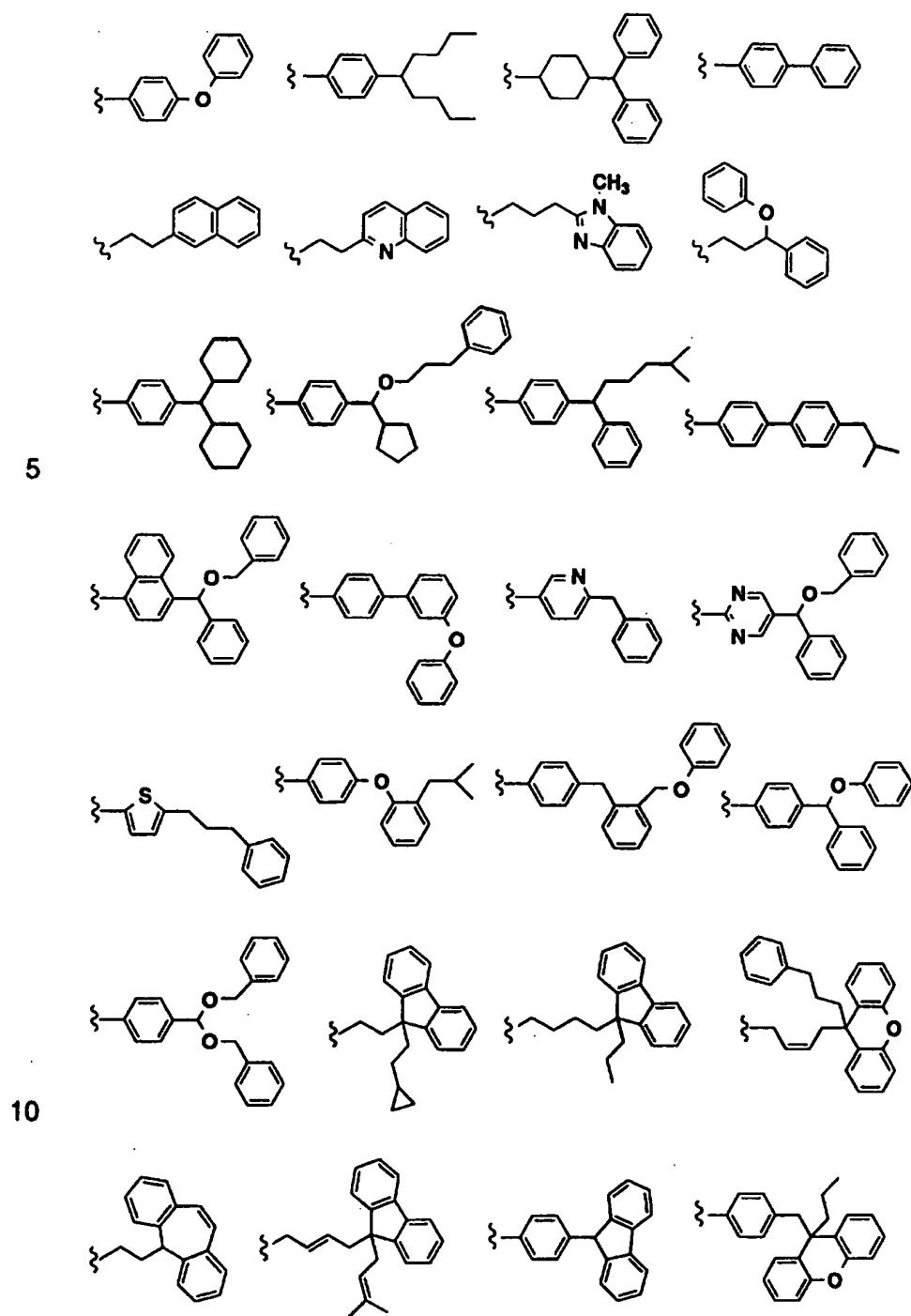
Table C

(Where W is H, H or O)

5

Examples of R¹

15

Table C (continued)

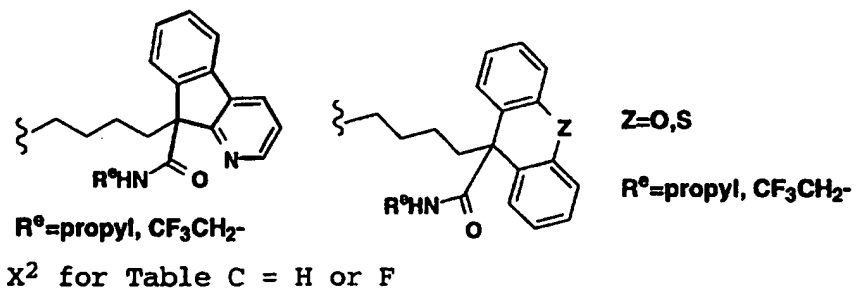
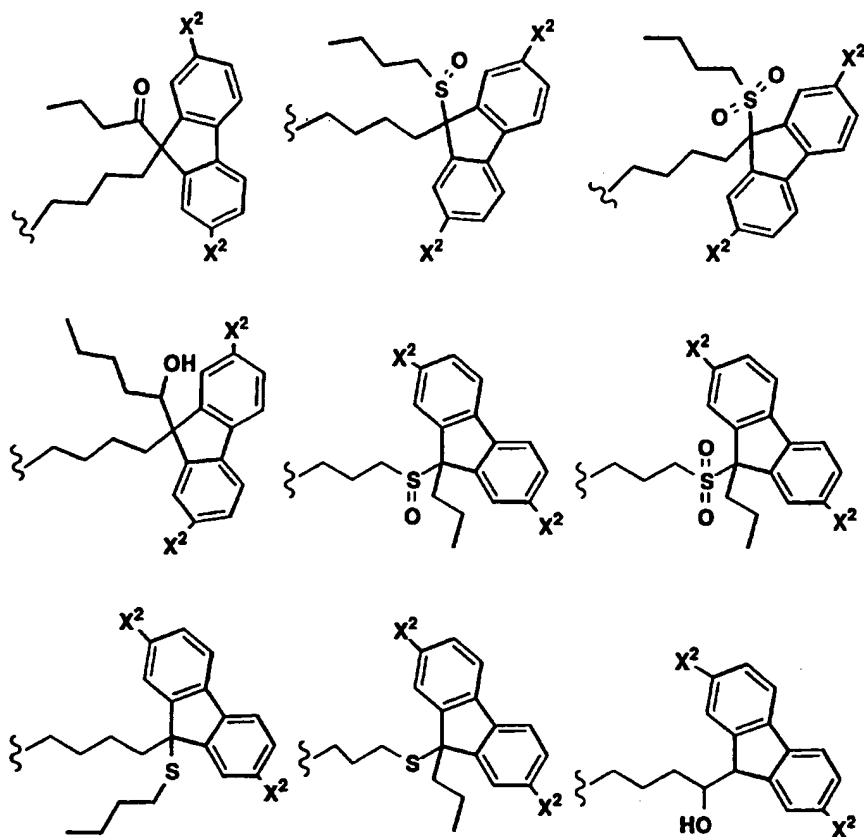


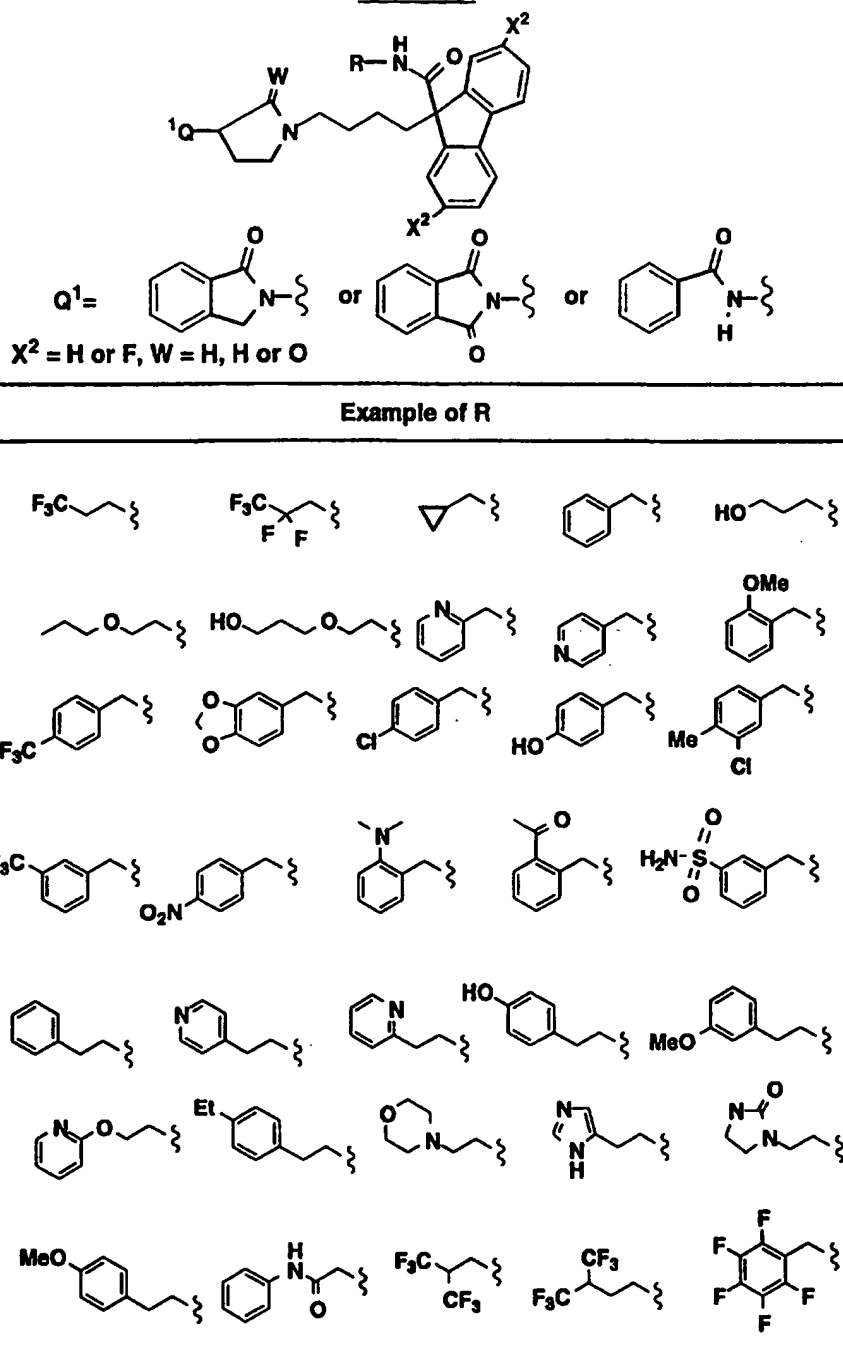
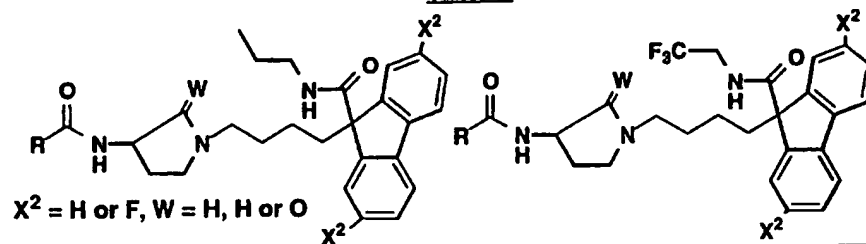
Table D

Table E



Example of R

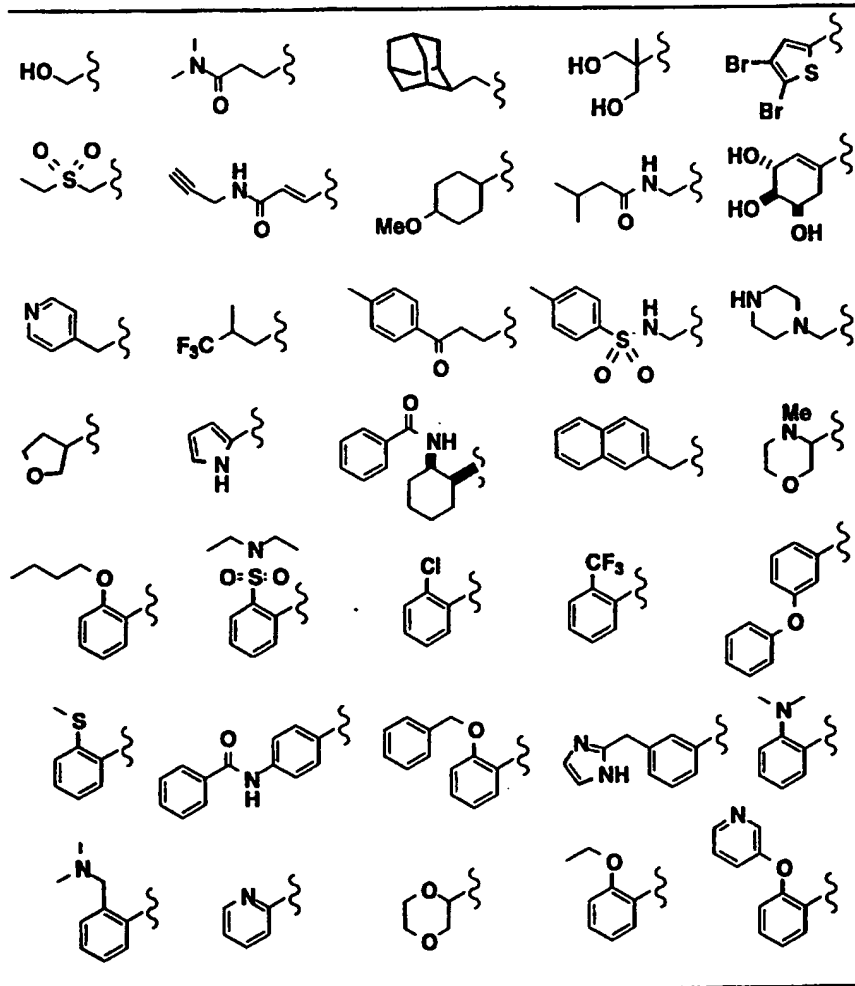


Table E (Cont'd)

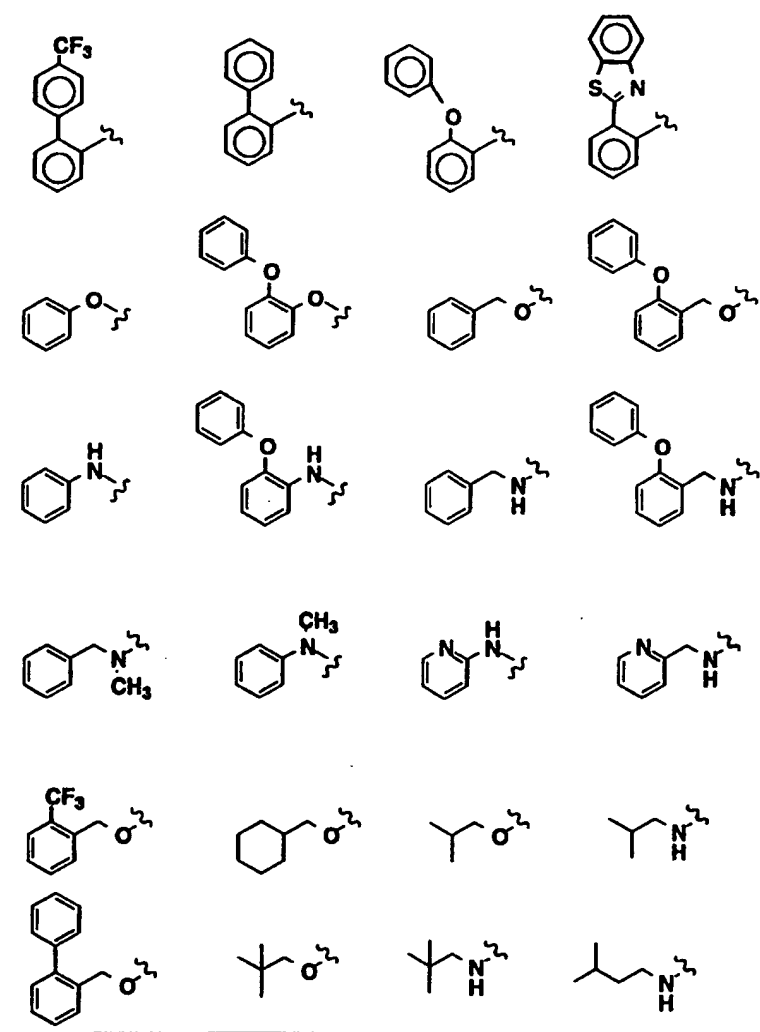
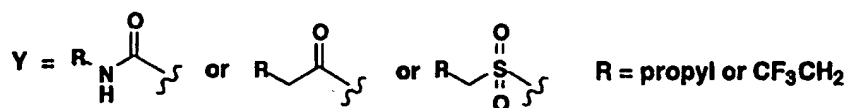
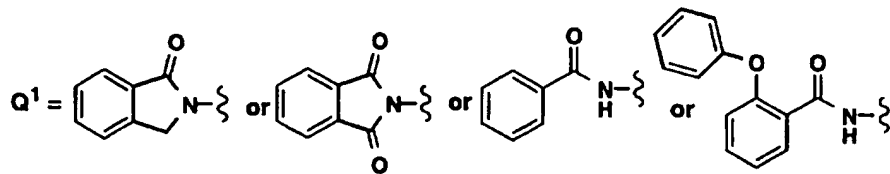
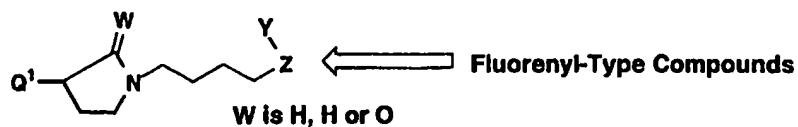


Table F



Fluorenyl-Type Rings: Z =

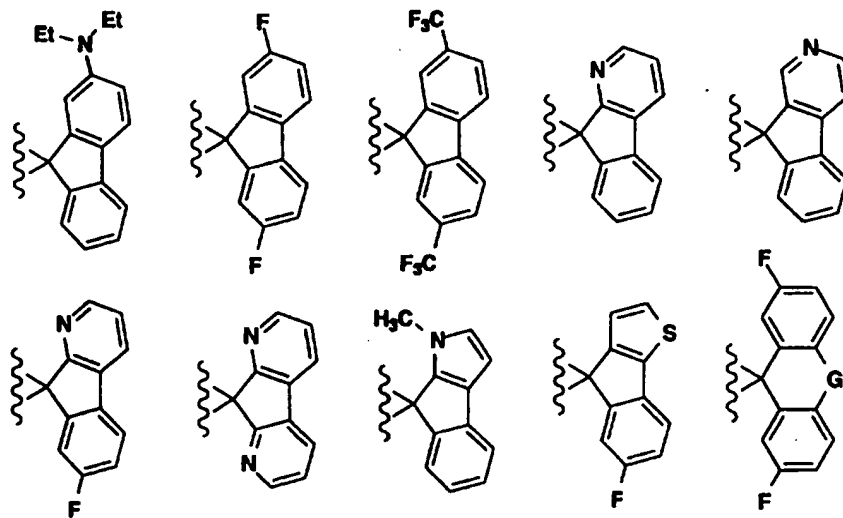
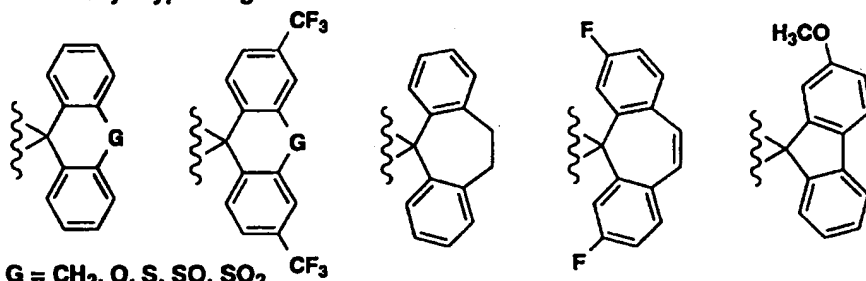
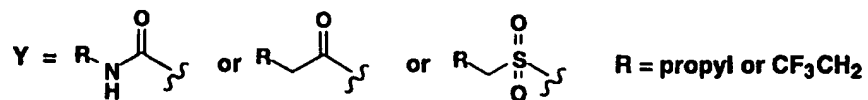
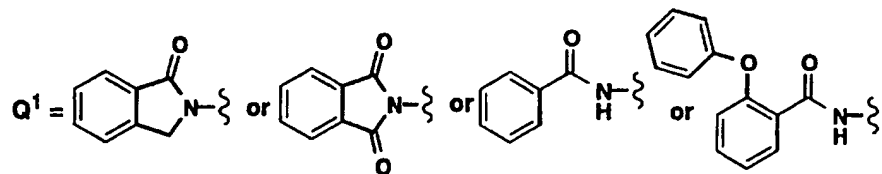
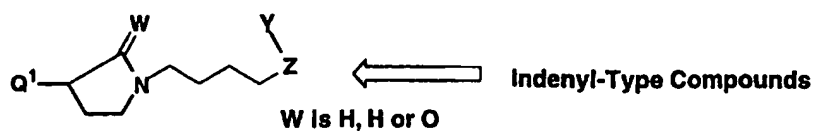


Table G



Indenyl-Type Rings: Z =

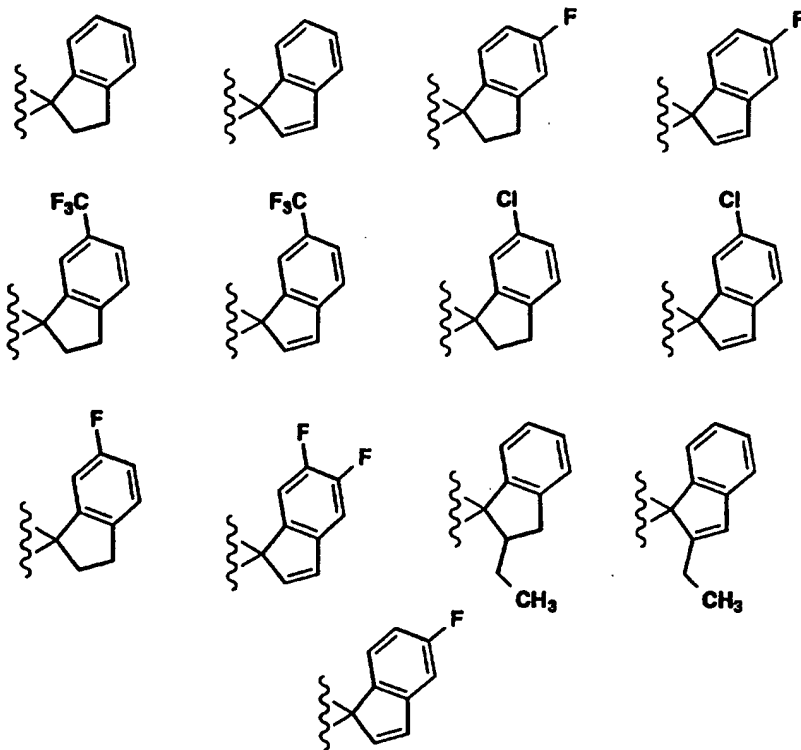


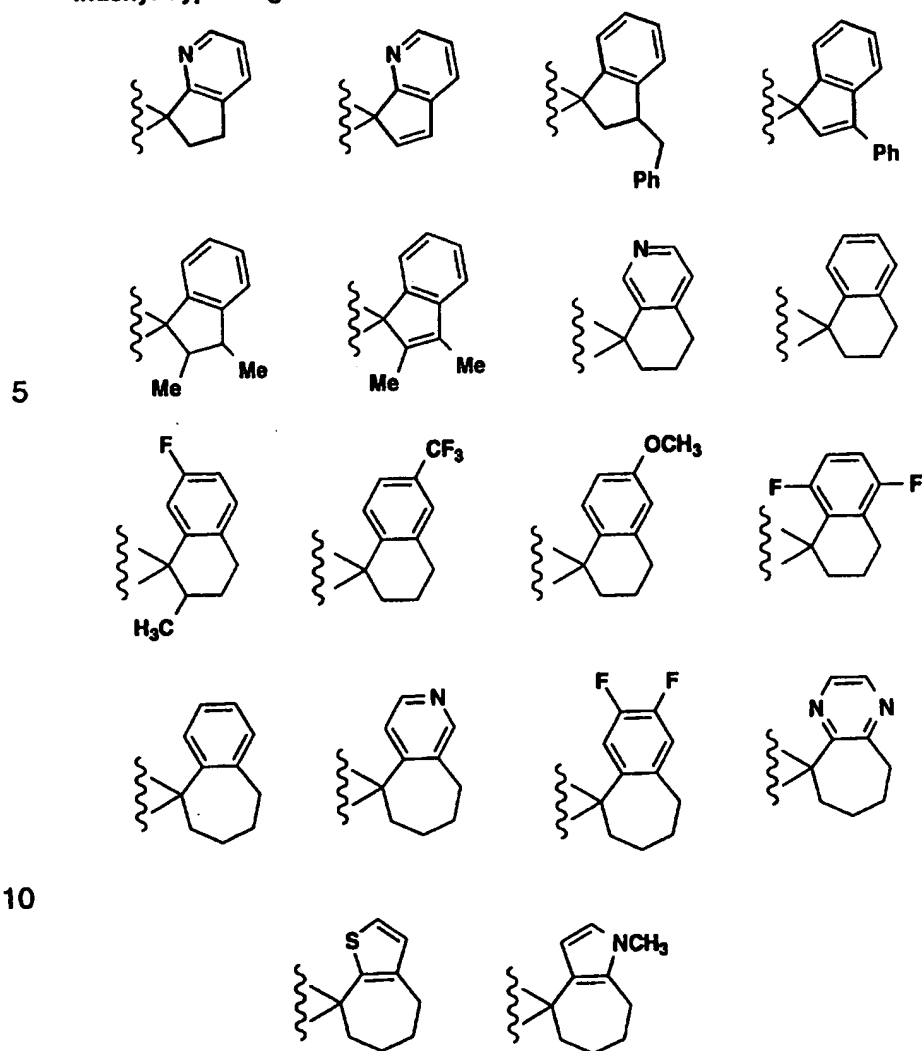
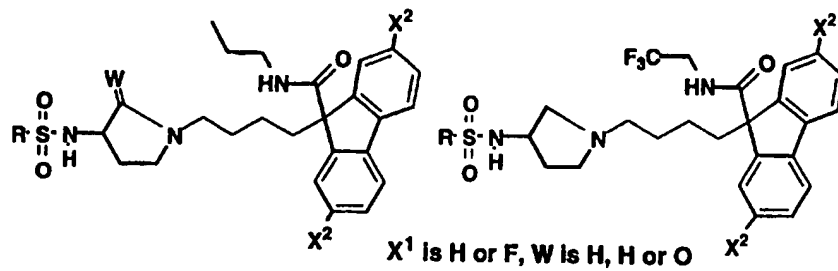
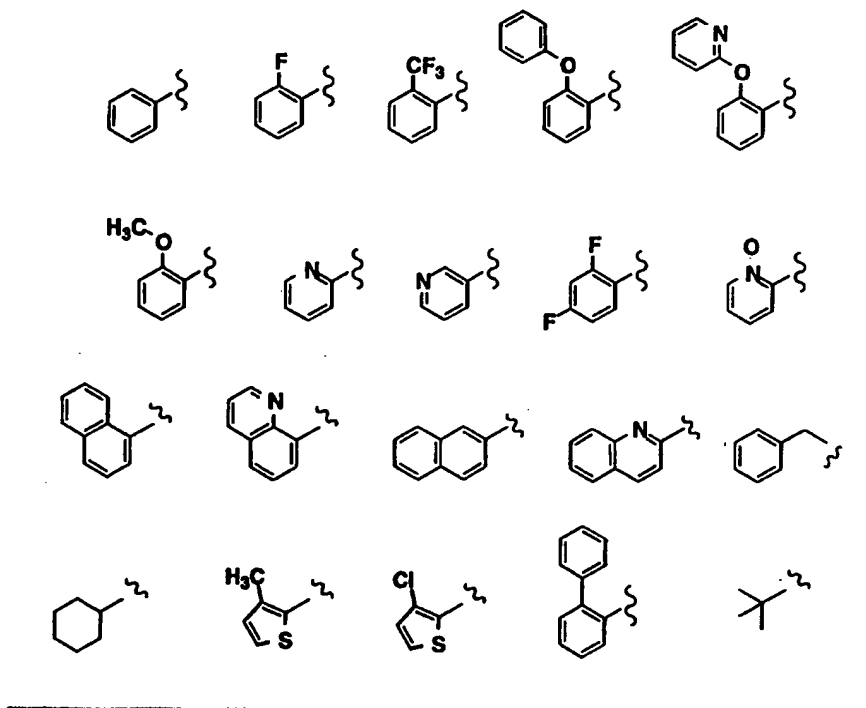
Table G (cont'd)**Indenyl-Type Rings: Z =**

Table H



Example of R



Example 337

5 cis-9-[4-[3-(2,3-Dihydro-1H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, N-oxide

Example 338

10 2-[1-[4-[9-(Butylsulfonyl)-9H-fluoren-9-yl]butyl]-3-pyrrolidinyl]-2,3-dihydro-1H-isoindol-1-one

Example 339

15 9-[4-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-1-pyrrolidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

Example 340

20 9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

Example 341

25 9-[4-[[3-(Benzoylamino)-1-pyrrolidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

Example 342

30 9-[4-[[3-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

Example 343

35 2,7-Difluoro-9-[4-[[3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

Example 344

9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

5

Example 345

2,3-Dihydro-2-[1-[4-[9-(1-oxopentyl)-9H-fluoren-9-yl]butyl]-3-pyrrolidinyl]-1H-isoindol-1-one, monohydrochloride

10

Example 346

2,3-Dihydro-2-[1-(1-oxo-3,3-diphenylpropyl)-3-pyrrolidinyl]-1H-isoindol-1-one

15

Example 347

[1-[4-[9-[(Propylamino)carbonyl]-9H-fluoren-9-yl]-butyl]-3-pyrrolidinyl]carbamic acid, phenylmethyl ester, monohydrochloride

20

Example 348

9-[4-[3-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, hydrochloride salt

25

Example 349

9-[4-[3-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, hydrochloride salt

30

Example 350

9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide

Example 351

35

9-[4-[3-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-pyrrolidinyl]-butyl]-N-propyl-9H-fluorene-9-carboxamide

Example 352

9-[4-[3-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-(2,2,3,3,4,4,4-heptafluorobutyl)-9H-fluorene-9-carboxamide, monohydrochloride

5

Example 353

9-[4-[[3-[(1,1-Dimethylethoxy)carbonyl]amino]-1-pyrrolidinyl]butyl]-3,6-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

10

Example 354

1-[4-[3-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-2-methyl-N-(2,2,2-trifluoroethyl)-1H-indene-1-carboxamide

Example 355

15

9-[4-[3-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-(2,2,3,3,3-pentafluoropropyl)-9H-fluorene-9-carboxamide, monohydrochloride

Example 356

20

1-[4-[3-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-1H-indene-1-carboxamide

Example 357

25

9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]butyl]-3,6-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

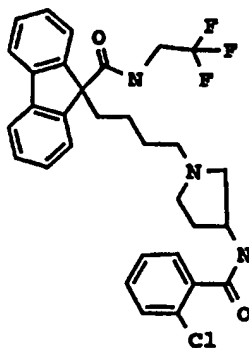
Example 358

3,6-Difluoro-9-[4-[3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

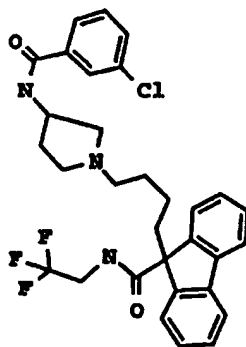
Please note that in the Examples 359 to 477 for structures bearing only two single bonded substituents to nitrogen, the third substituent is always hydrogen, but it is not shown explicitly in the structures. Also, please note that in the Examples 359 to 475 for structures bearing oxygen and sulfurs with only one single bonded substituent, the second substituent is always hydrogen, but is not shown explicitly in the structures.

Example No.

359

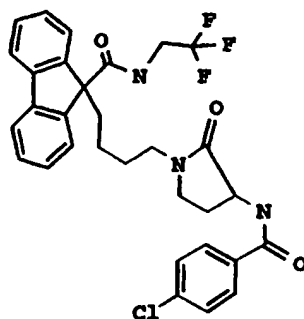


360

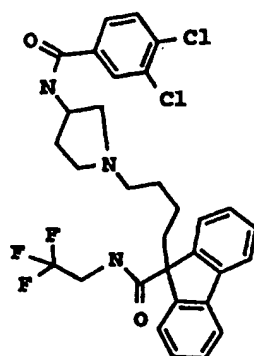


15

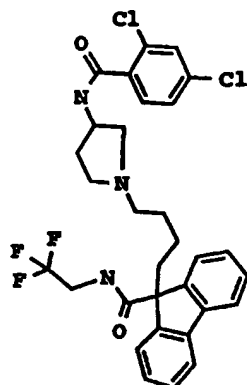
361



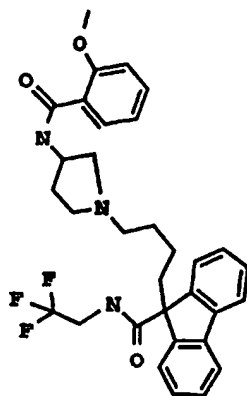
362



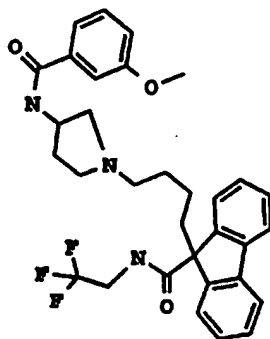
363



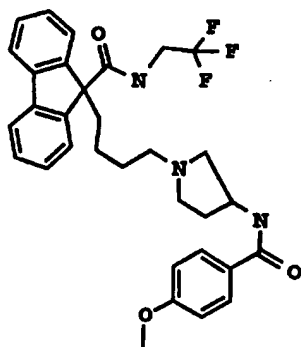
364



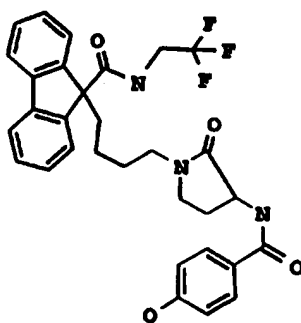
365



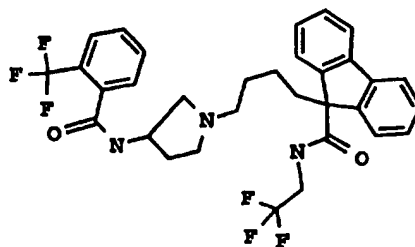
366



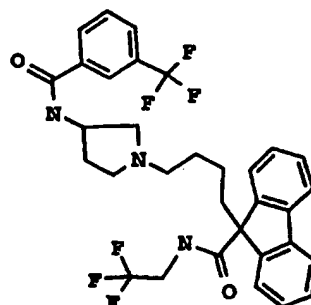
367



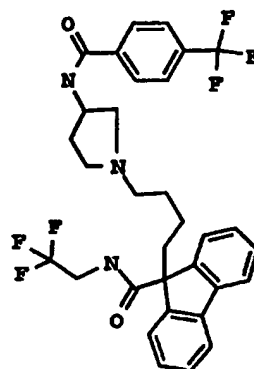
368



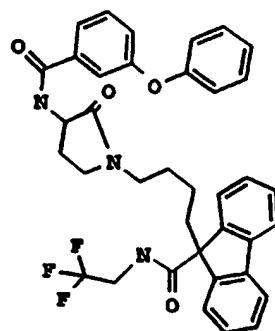
369



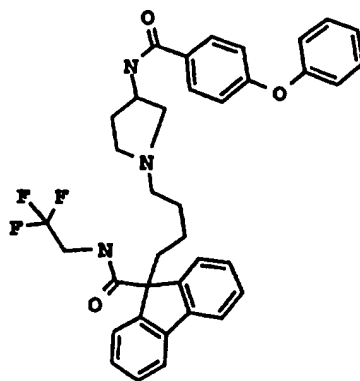
370



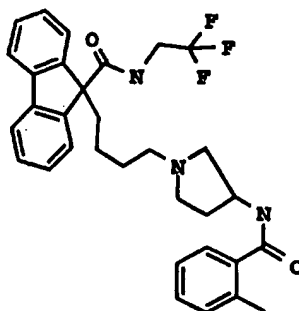
371



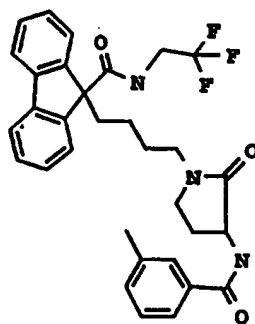
372



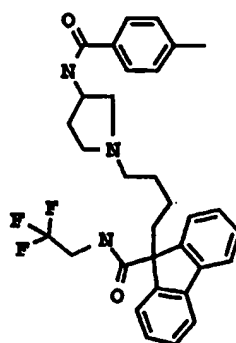
373



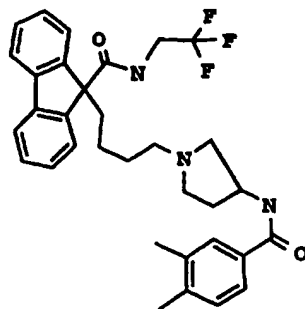
374



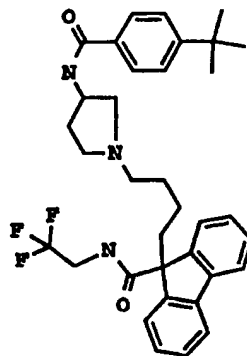
375



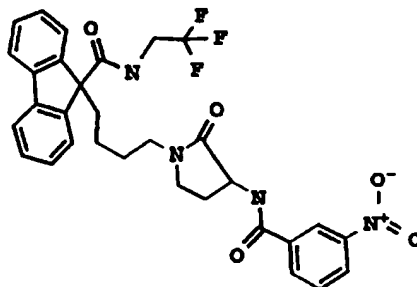
376



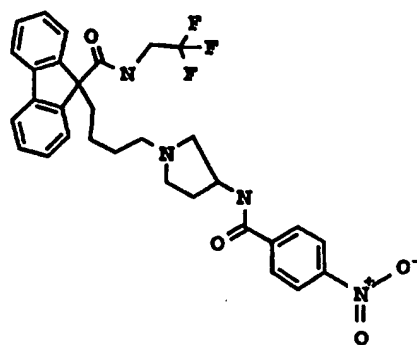
377



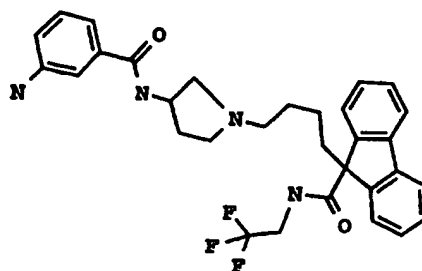
378



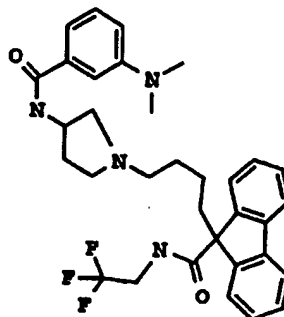
379



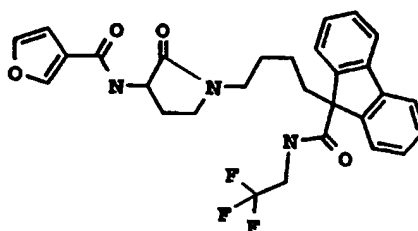
380



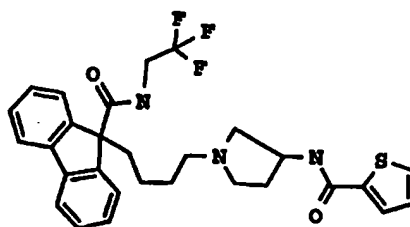
381



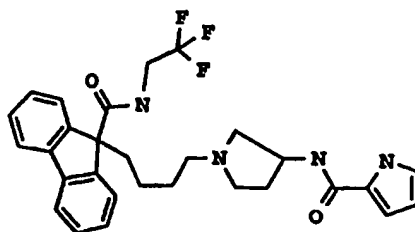
382



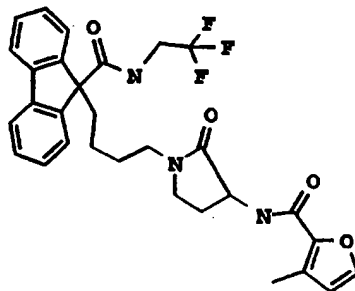
383



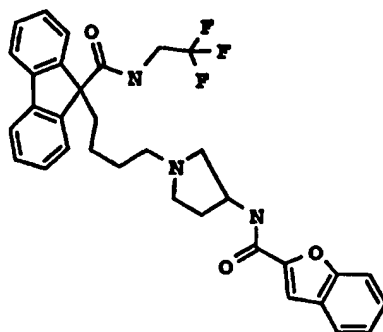
384



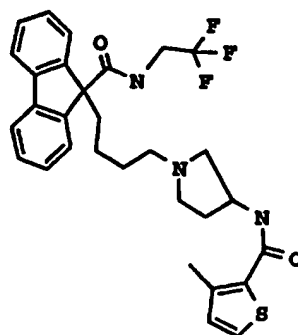
385



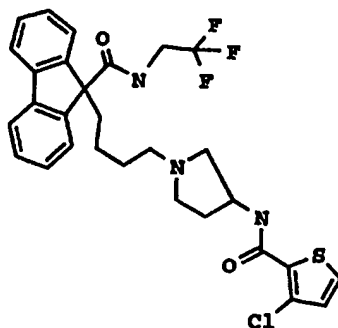
386



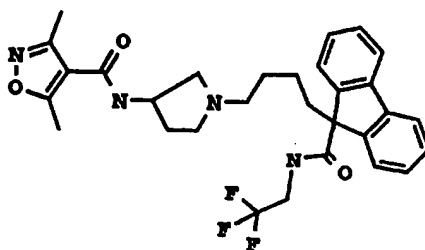
387



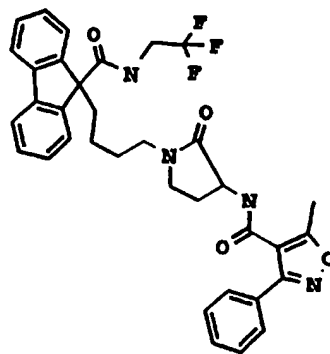
388



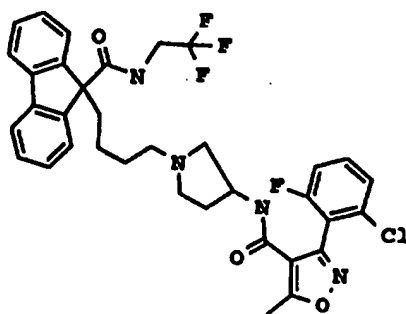
389



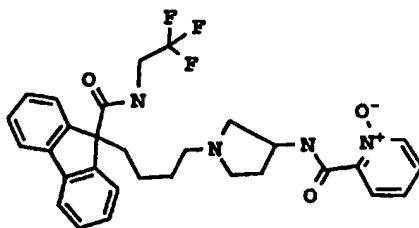
390



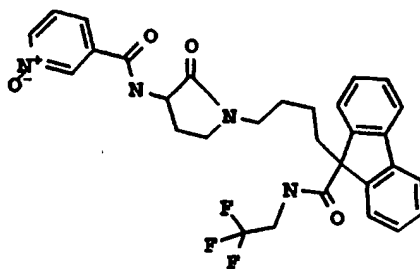
391



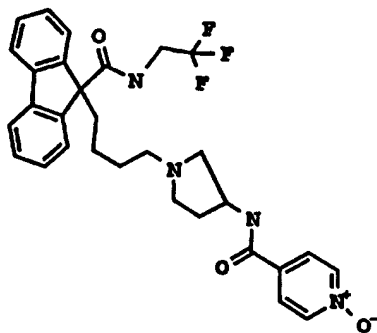
392



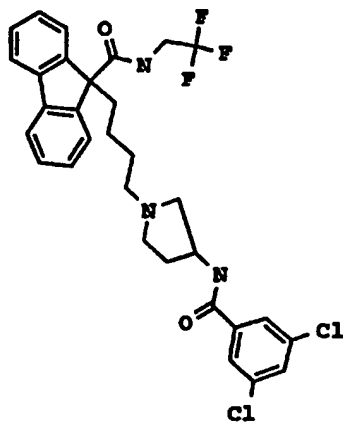
393



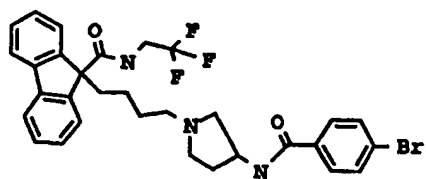
394



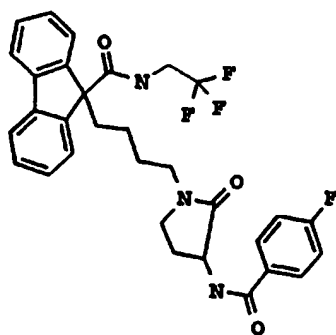
395



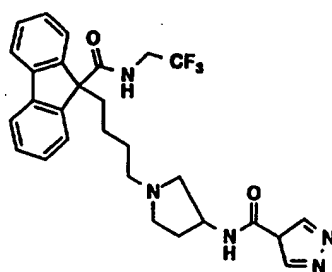
396



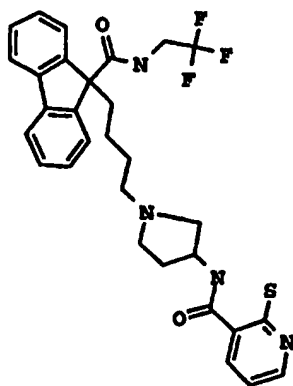
397



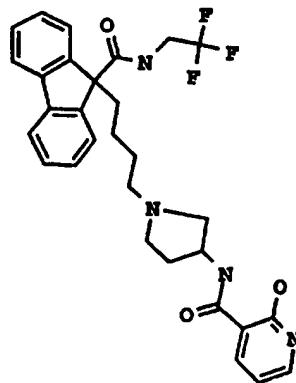
398



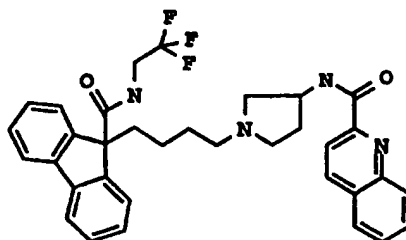
399



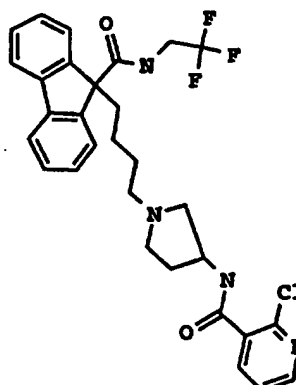
400



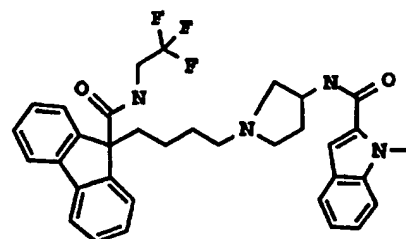
401



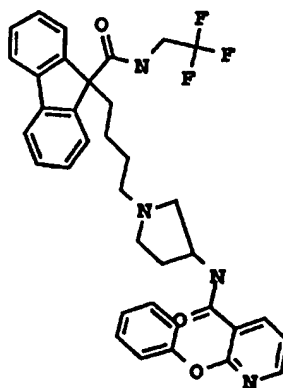
402



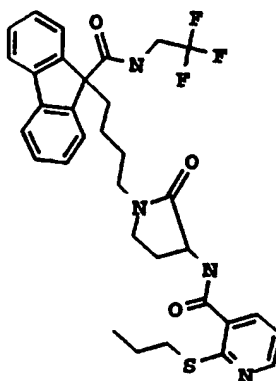
403



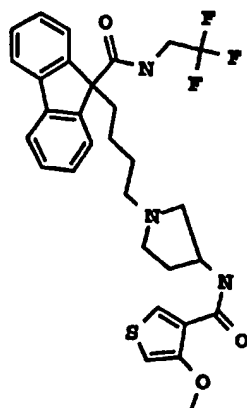
404



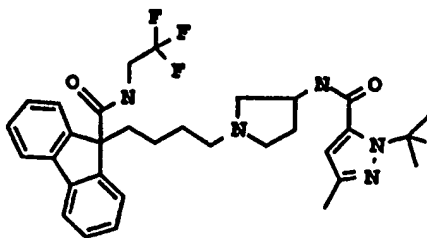
405



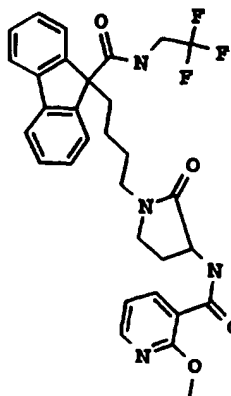
406



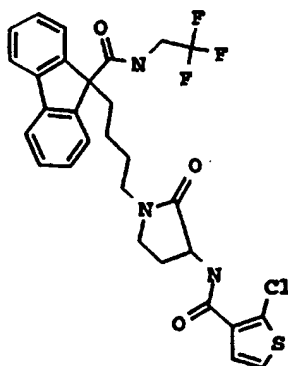
407



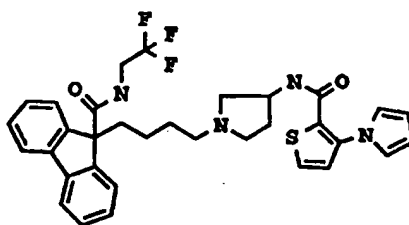
408



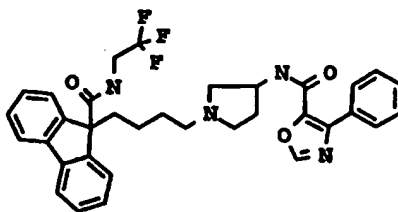
409



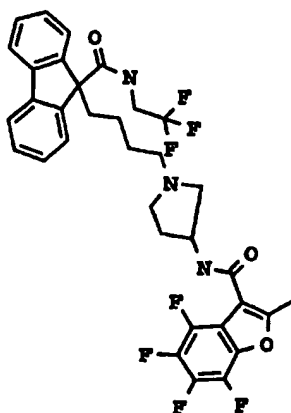
410



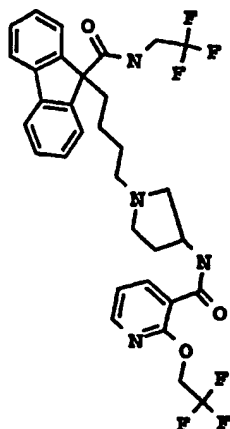
411



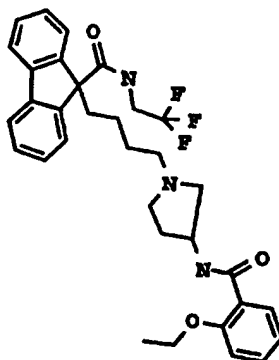
412



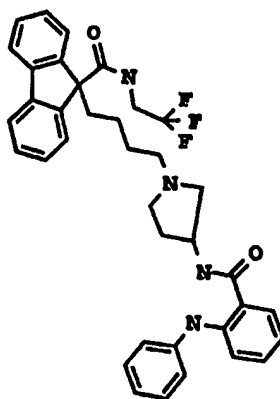
413



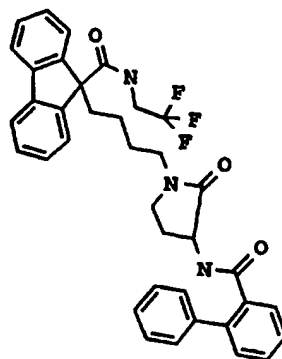
414



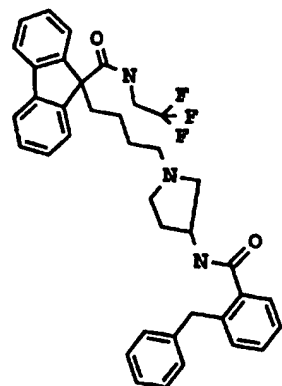
415



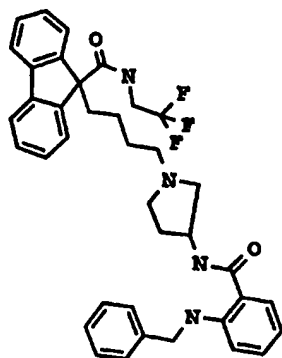
416



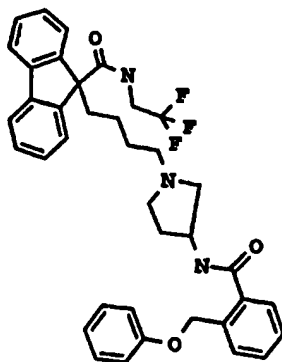
417



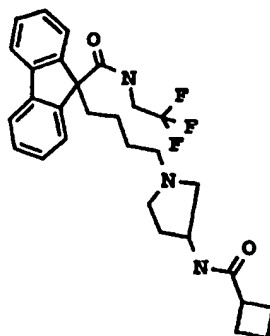
418



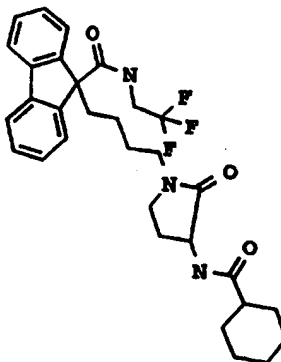
419



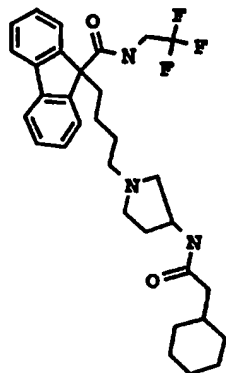
420



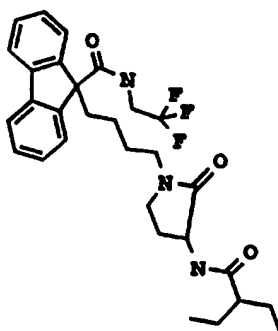
421



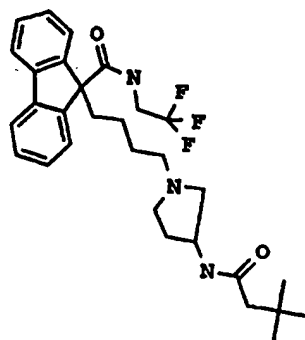
422



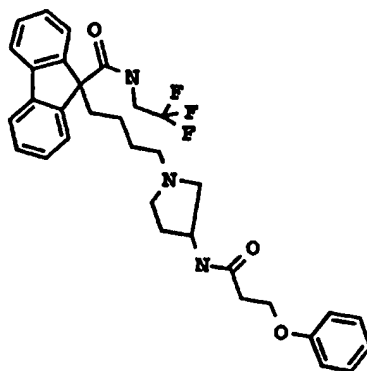
423



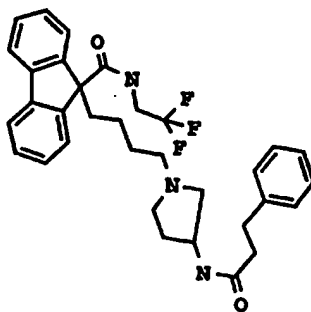
424



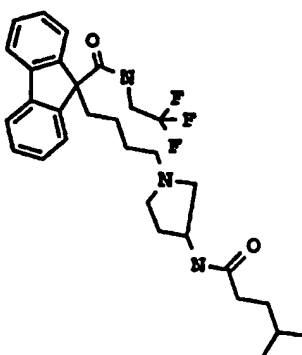
425



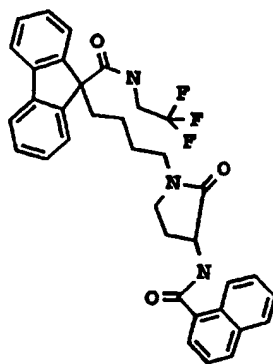
426



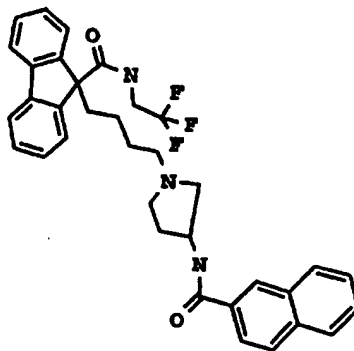
427



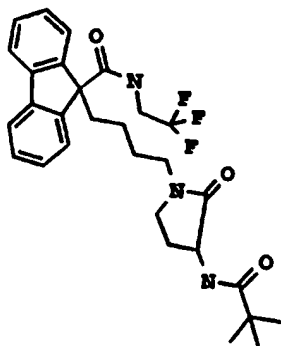
428



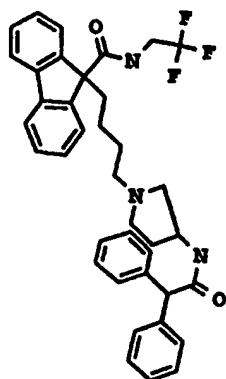
429



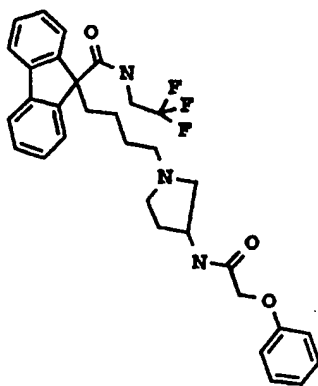
430



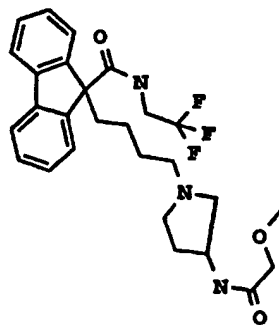
431



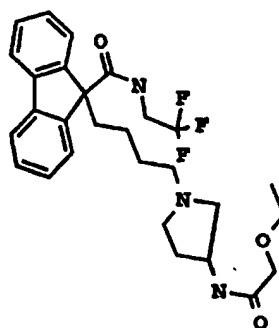
432



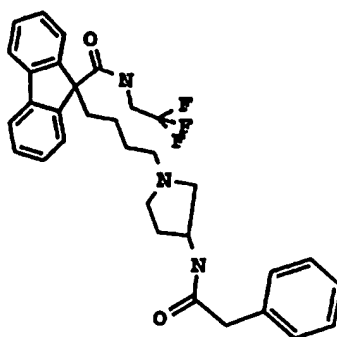
433



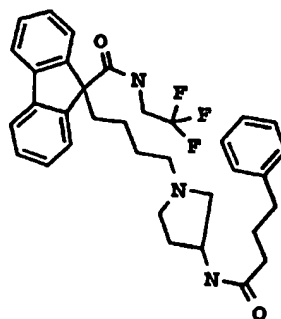
434



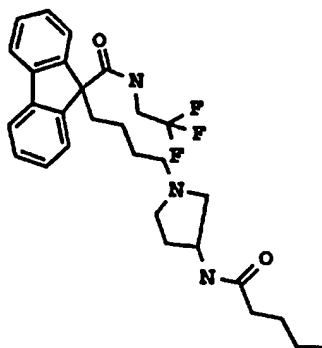
435



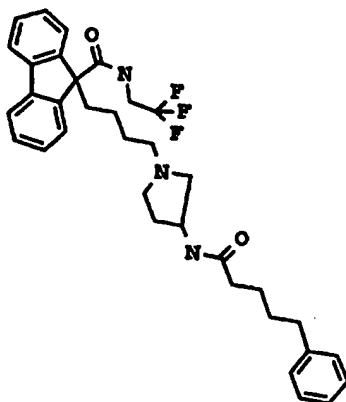
436



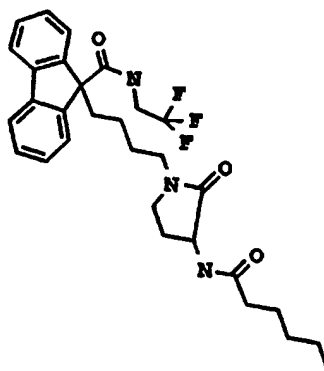
437



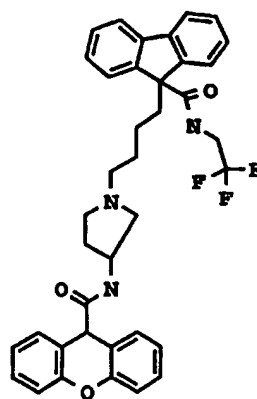
438



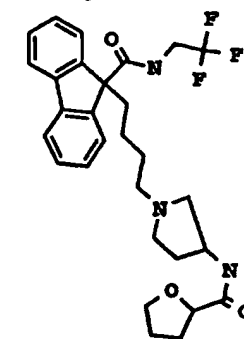
439



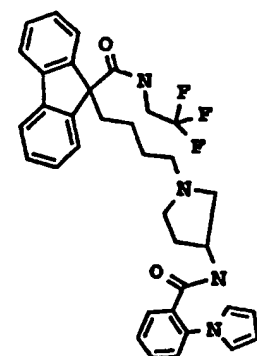
440



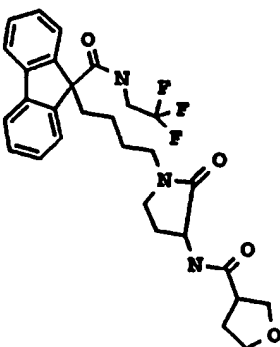
441



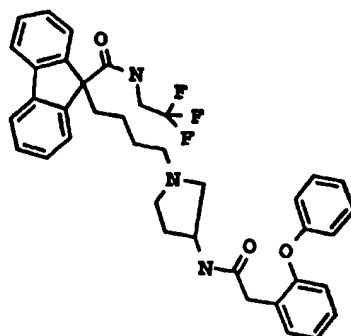
442



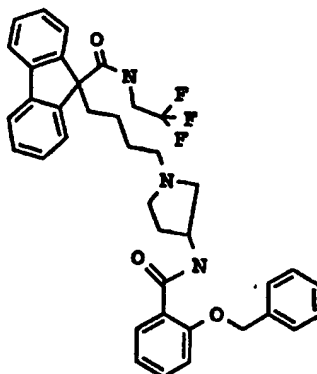
443



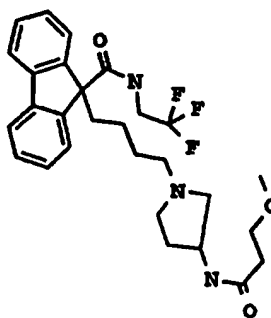
444



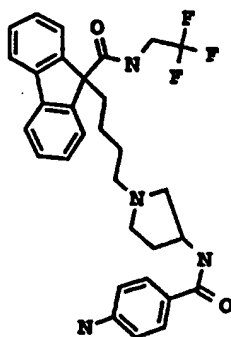
445



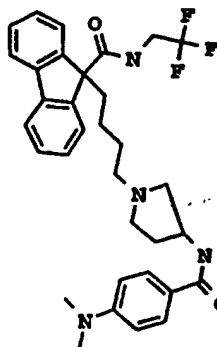
446



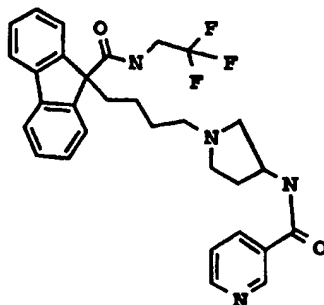
447



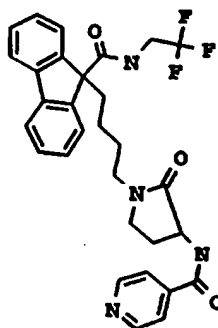
448



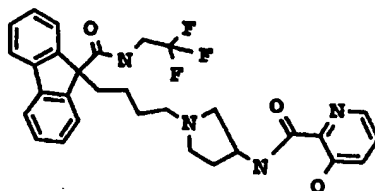
449



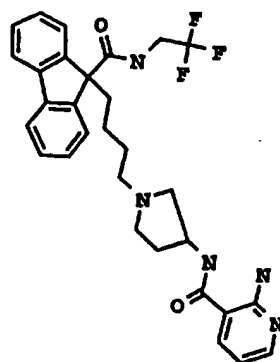
450



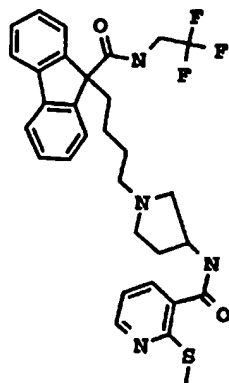
451



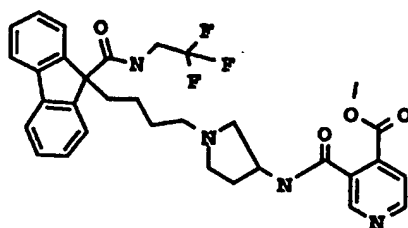
452



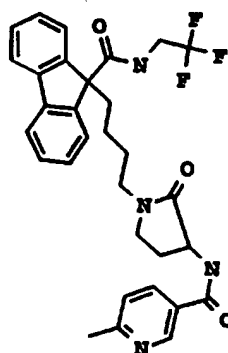
453



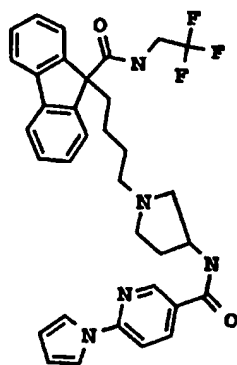
454



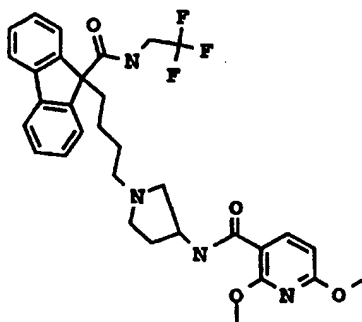
455



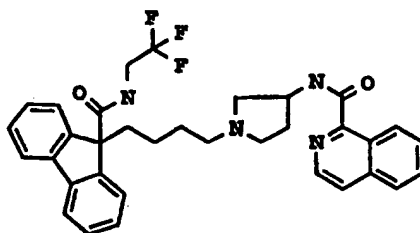
456



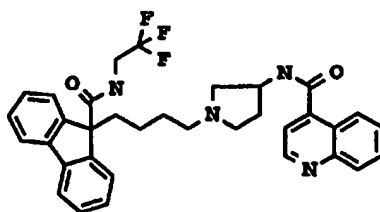
457



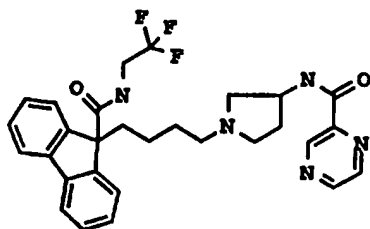
458



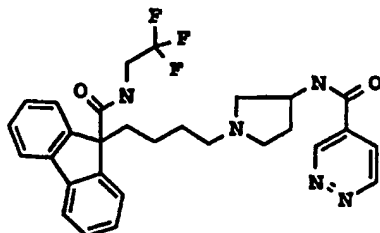
459



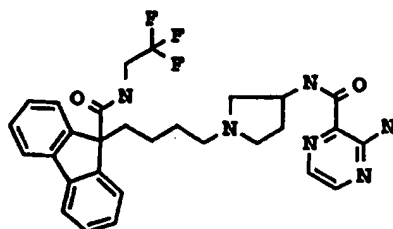
460



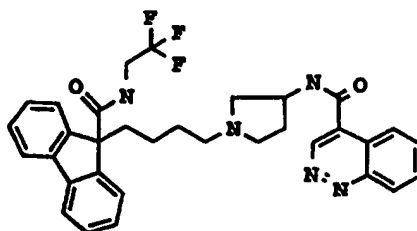
461



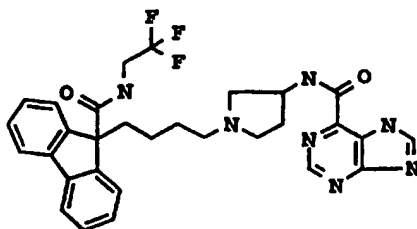
462



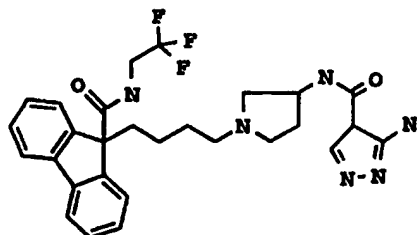
463



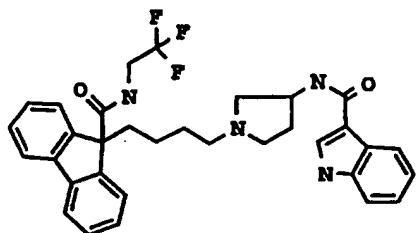
464



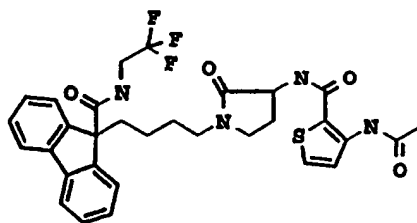
465



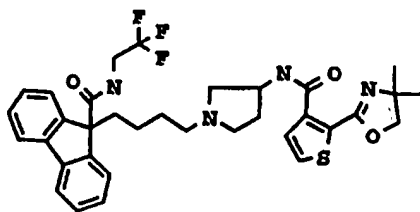
466



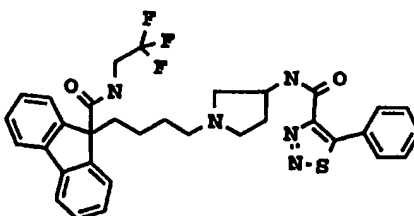
467



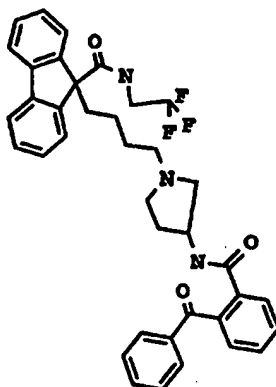
468



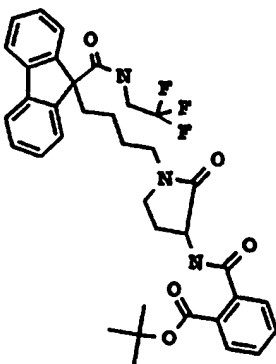
469



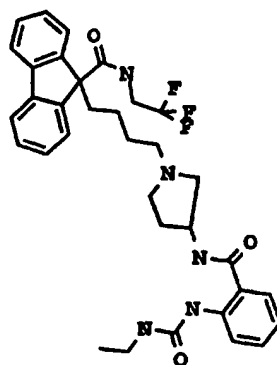
470



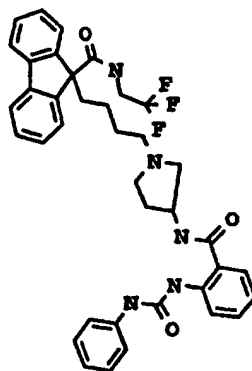
471



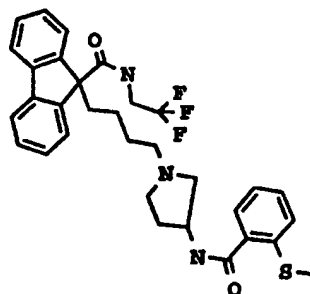
472



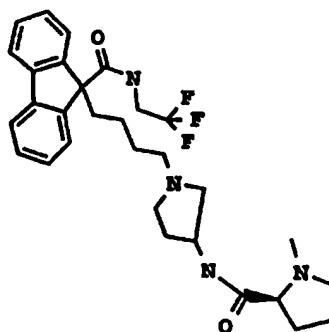
473



474



475

**Example 476**

9-[4-[3-[(Phenoxycarbonyl)amino]-1-pyrrolidinyl]-
butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-
carboxamide, monohydrochloride

5

Example 477

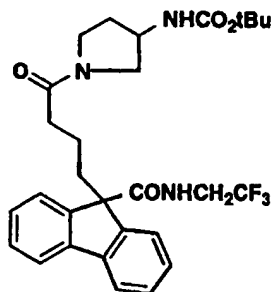
9-[4-[3-[[(Phenylamino)carbonyl]amino]-1-pyrrol-
idinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-
fluorene-9-carboxamide, monohydrochloride

10

Example 478

9-[4-[3-[(Phenylsulfonyl)amino]-1-pyrrolidinyl]-
butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-
carboxamide, monohydrochloride

15

Example 479Example 480

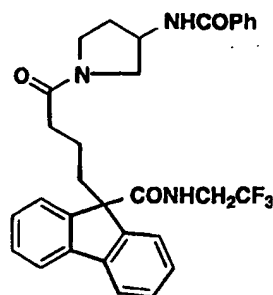
20

cis-9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-
pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-
9H-fluorene-9-carboxamide, N-oxide

Example 481

25

9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]-
4-oxobutyl]-N-(2,2,2-trifluoroethyl)-9H-
fluorene-9-carboxamide

Example 482

5

Example 483

9-[4-[3-[[(1,1-Dimethylethoxy) carbonyl] amino]-1-pyrrolidinyl]pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

10

Example 484

9-[4-[3-[[(2-Phenoxyphenyl) sulfonyl] amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

15

Example 485

[1-[[[2-[9-[[(2,2,2-Trifluoroethyl) amino] carbonyl]-9H-fluorene-9-yl]ethyl]amino]carbonyl]-3-pyrrolidin-yl]carbamic acid, 1,1-dimethylethyl ester

20

Example 486

9-[2-[[[3-(Benzoylamino)-1-pyrrolidinyl] carbonyl]-amino]ethyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

25

Example 487

3-[[(1,1-Dimethylethoxy) carbonyl] amino]-1-pyrrolidinecarboxylic acid, 2-[9-[[(2,2,2-trifluoroethyl) amino] carbonyl]-9H-fluorene-9-yl], ethyl ester

30

Example 488

3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidine-
carboxylic acid, 2-[9-[[(2,2,2-trifluoroethyl)-
amino]carbonyl]-9H-fluoren-9-yl]ethyl ester

5

Example 489

9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]-
pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-
carboxamide, monohydrochloride

10

Example 490

9-[2-[[[3-[(2-Phenoxybenzoyl)amino]-1-
pyrrolidinyl]carbonyl]amino]ethyl]-N-(2,2,2-
trifluoroethyl)-9H-fluorene-9-carboxamide

15

Example 491

3-(Benzoylamino)-1-pyrrolidinecarboxylic acid,
2-[9-[[(2,2,2-trifluoroethyl)amino]carbonyl]-
9H-fluoren-9-yl]ethyl ester

20

Example 492

9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]pentyl]-
N-(2,2,2-trifluoroethyl)-9H-fluorene-9-
carboxamide, monohydrochloride

25

Example 493

9-[4-[3-[[(1,1-Dimethylethoxy)carbonyl]amino]-
1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-
9H-thioxanthene-9-carboxamide

30

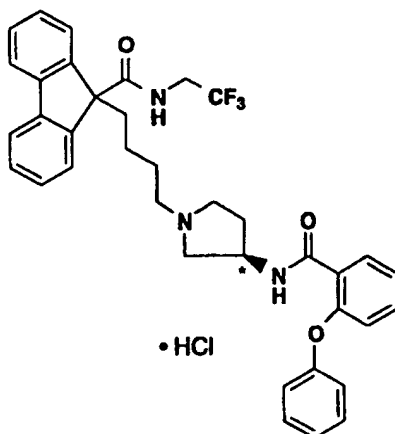
Example 494

9-[4-[3-(Benzoylamino)-1-pyrrolidinyl]-
butyl]-N-(2,2,2-trifluoroethyl)-9H-
thioxanthene-9-carboxamide

Example 495

9-[4-[3-[[(2-Phenoxyphenyl) carbonyl] amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-thioxanthene-9-carboxamide

5

Example 496

(R)-9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

m.p. 112-115°C

10 MS (ES, + ions): m/z 628 (M+H)

Anal. Calcd for $C_{37}H_{36}F_3N_3O_3 + 1.0 \text{ HCl} + 0.9 \text{ H}_2\text{O}$:

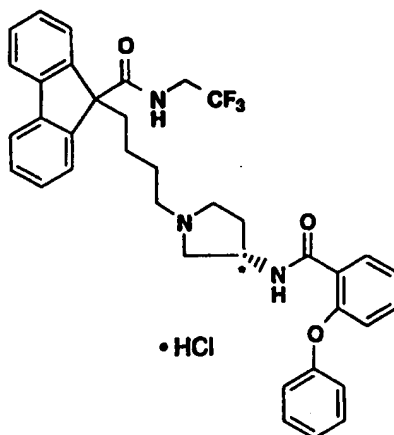
C, 65.32; H, 5.75; N, 6.18; F, 8.38;

Cl, 5.21

Found: C, 65.30; H, 5.59; N, 6.01; F, 8.83;

15

Cl, 5.35.

Example 497

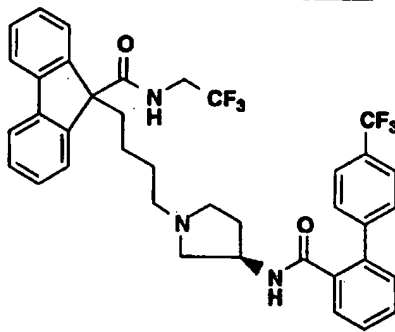
(S)-9-[4-[3-[(2-Phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

m.p. 98-103°C

MS (ES, + ions): m/z 628 (M+H).

- 5 Anal. Calcd for $C_{37}H_{36}F_3N_3O_3 + 1.0 \text{ HCl} + 1.5 \text{ H}_2\text{O}$:
 C, 64.30; H, 5.83; N, 6.08; F, 8.25
 Found: C, 64.34; H, 5.63; N, 5.90; F, 8.46.

Example 498



• HCl

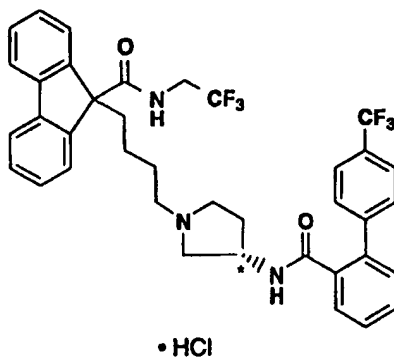
10

R isomer
 (R)-N-(2,2,2-Trifluoroethyl)-9-[4-[3-[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-pyrrolidinyl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.

m.p. 108-112°C

MS (ES, + ions): m/z 680 (M+H)

- 15 Anal. Calcd for $C_{38}H_{35}F_6N_3O_2 + 1.3 \text{ HCl} + 2.1 \text{ H}_2\text{O}$:
 C, 59.67; H, 5.34; N, 5.49; Cl, 6.03
 Found: C, 59.75; H, 5.00; N, 5.18; Cl, 5.75.

Example 499

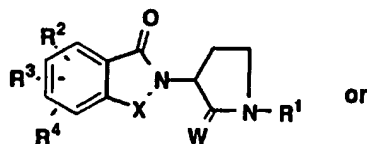
S isomer
(S)-N-(2,2,2-Trifluoroethyl)-9-[4-{3-[[4'-(1,1,1-trifluoromethyl)][1,1'-biphenyl]-2-yl]carbonyl]amino]-1-pyrrolidinyl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.

5 m.p. 101-105°C

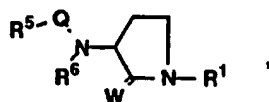
MS (ES, + ions): m/z 680 (M+H).

What Is Claimed Is:

1. A compound which has the structure



5



where Q is $\text{--}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{--}$ or $\text{--}\overset{\text{O}}{\underset{\text{O}}{\text{S}}}\text{--}$;

W is H, H or O;

10

X is: CHR^8 , $\text{--}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{--}$, $\text{--}\underset{\text{R}^9}{\text{CH}}\text{--}\underset{\text{R}^{10}}{\text{CH}}\text{--}$ or $\text{--}\underset{\text{R}^9}{\text{C}}=\underset{\text{R}^{10}}{\text{C}}\text{--}$;

R^8 , R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

15

R^1 is alkyl, alkenyl, alkynyl, aryl, heteroaryl, arylalkyl, diarylalkyl, arylalkenyl, diarylalkenyl, arylalkynyl, diarylalkynyl, diarylalkylaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl, all optionally substituted

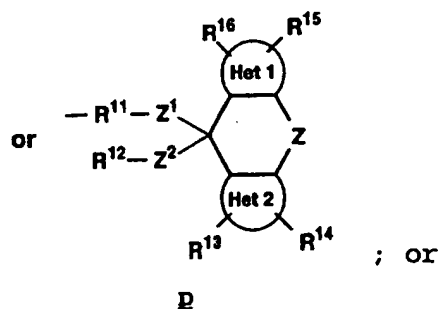
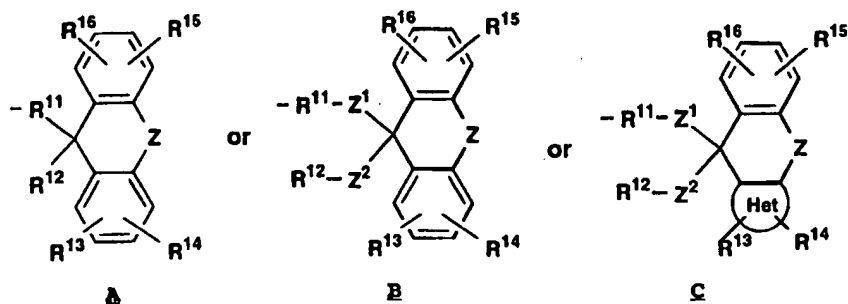
20

through available carbon atoms with 1, 2, 3 or 4 groups selected from halo, haloalkyl, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, fluorenyl,

25

heteroarylalkyl, hydroxy or oxo;

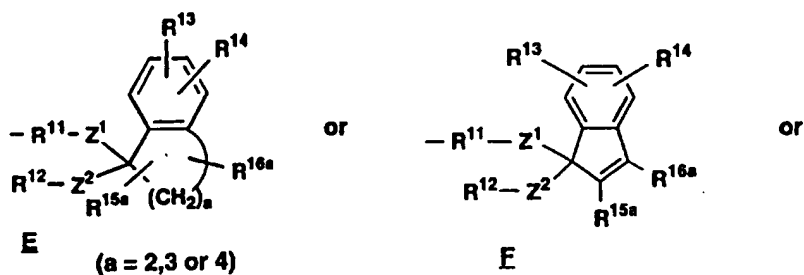
or R^1 is a fluorenyl-type group of the structure



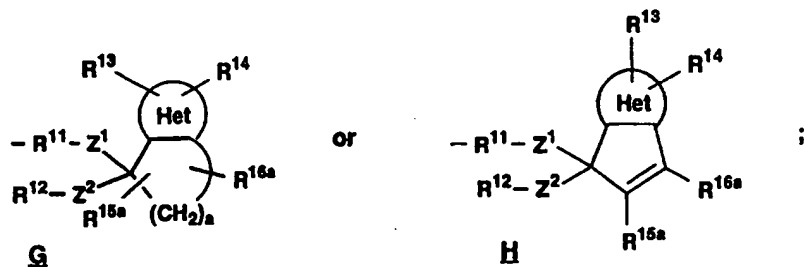
5

D

R^1 is an indenyl-type group of the structure

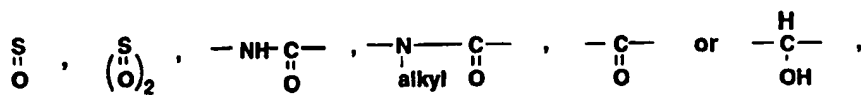


10



15

Z^1 and Z^2 are the same or different and are independently a bond, O, S,



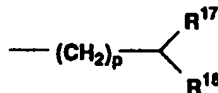
with the proviso that with respect to B, at least one of Z¹ and Z² will be other than a bond; R¹¹ is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms; arylene or mixed arylene-alkylene; R¹² is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl, with the provisos that

(1) when R¹² is H, aryloxy, alkoxy or arylalkoxy, then Z² is $\begin{array}{c} \text{—NH—C—} \\ \parallel \\ \text{O} \end{array}$, $\begin{array}{c} \text{—N—C—} \\ | \quad \parallel \\ \text{alkyl O} \end{array}$, $\begin{array}{c} \text{—C—} \\ \parallel \\ \text{O} \end{array}$ or a bond and

(2) when Z² is a bond, R¹² cannot be heteroaryl or heteroarylalkyl;

Z is bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene from 1 to 5 carbon atoms; R¹³, R¹⁴, R¹⁵, and R¹⁶ are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cyclo-heteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl or aryloxy; R^{15a} and R^{16a} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cyclo-heteroalkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

or R¹ is a group of the structure

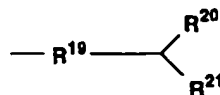


wherein p is 1 to 8 and R¹⁷ and R¹⁸ are each independently H, alkyl, alkenyl, aryl, arylalkyl,

heteroaryl, heteroarylalkyl, cycloalkyl or cycloalkylalkyl at least one of R¹⁷ and R¹⁸ being other than H;

or R¹ is a group of the structure

5



wherein R¹⁹ is aryl or heteroaryl;

R²⁰ is aryl or heteroaryl;

R²¹ is H, alkyl, aryl, alkylaryl, arylalkyl,

10 aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heteroarylalkoxy, cycloalkyl, cycloalkylalkyl or cycloalkylalkoxy;

R², R³, R⁴ are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl,

15 arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

R⁵ is independently alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl,

20 arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy, cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkyl-

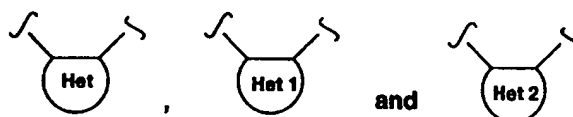
25 amino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl,

30 haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl,

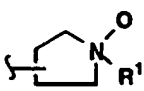
35 heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, thiol, alkylthio,

arylthio, heteroarylthio, arylthioalkyl,
 alkylcarbonyl, arylcarbonyl, arylaminocarbonyl,
 alkoxycarbonyl, aminocarbonyl, alkynylamino-
 carbonyl, alkylaminocarbonyl, alkenylamino-
 5 carbonyl, alkylcarbonyloxy, arylcarbonyloxy,
 alkylcarbonylamino, arylcarbonylamino, arylsul-
 finyl, arylsulfinylalkyl, arylsulfonyl, alkylsul-
 fonyl, arylsulfonylamino, heteroarylcarbonylamino,
 heteroarylsulfinyl, heteroarylthio, heteroaryl-
 10 sulfonyl, alkylsulfinyl;

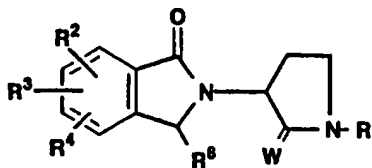
R^6 is hydrogen or C_1 - C_4 alkyl or C_1 - C_4
 alkenyl; all optionally substituted with 1, 2, 3
 or 4 groups which may independently be any of the
 substituents listed in the definition of R^5 set out
 15 above;



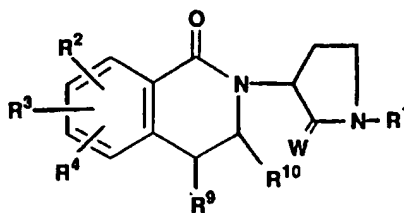
are the same or different and are independently
 selected from heteroaryl containing 5- or 6-ring
 20 members; and

an N-oxide  thereof; stereoisomers
 thereof; and a pharmaceutically acceptable salt
 thereof.

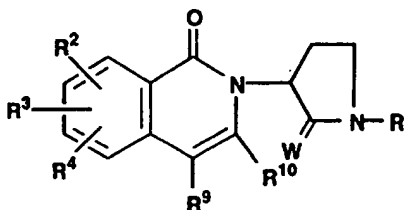
2. The compound as defined in Claim 1
 25 having the formula



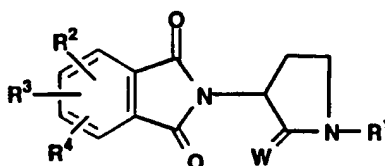
or



or

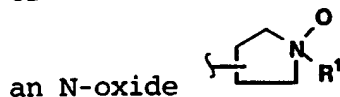


or



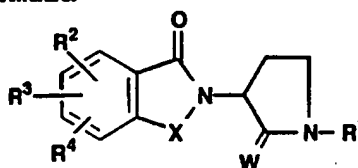
5

or



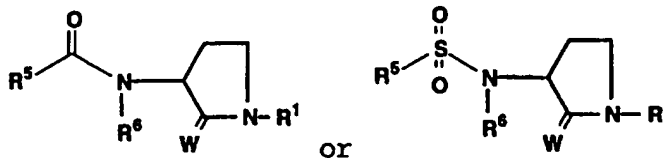
an N-oxide thereof, and a pharmaceutically acceptable salt thereof.

3. The compound as defined in Claim 1
10 having the formula

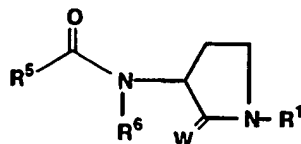


4. The compound as defined in Claim 3
where R¹ is arylalkyl, heteroalkylalkyl or
15 cycloalkyl-alkyl.

5. The compound as defined in Claim 1
having the formula

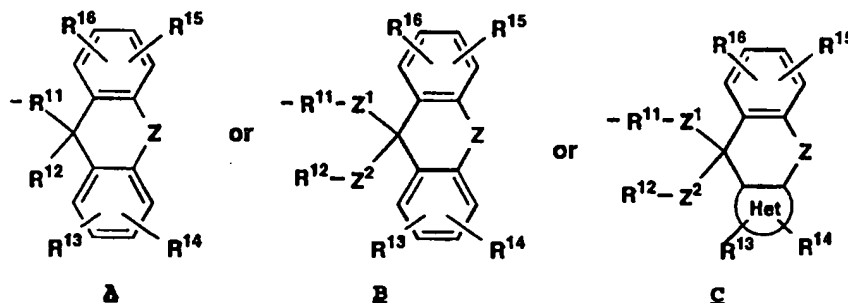


6. The compound as defined in Claim 1
having the formula

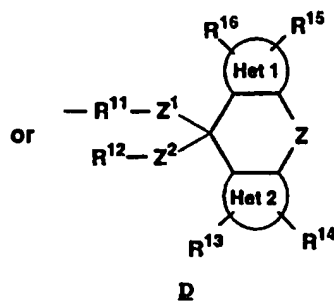


5

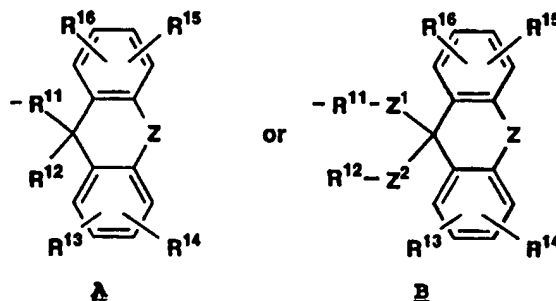
7. The compound as defined in Claim 1
wherein R¹ is



10



8. The compound as defined in Claim 7
wherein R¹ is



Z is a bond, O or S;

20

R¹³, R¹⁴, R¹⁵ and R¹⁶ are each H or one of
R¹⁵ and R¹⁶ and one of R¹³ and R¹⁴ are halogen;

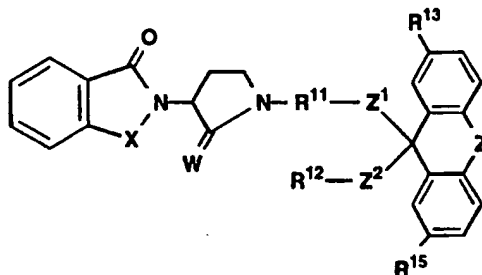
Z^1 is a bond or $C=O$;

R^{11} is alkylene or alkenylene;

$R^{12} - Z^2$ is $R^{12a} - NH - \overset{O}{\parallel} C -$; or $R^{12a} \overset{O}{\parallel} C -$;

R^{12a} is alkyl, fluorinated lower alkyl or
5 polyfluorinated lower alkyl.

9. The compound as defined in Claim 1
having the structure



10 Z is O, S or a bond;

R^{13} and R^{15} are independently H or F;

Z^1 is a bond;

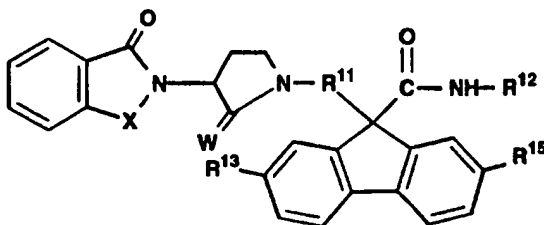
R^{11} is alkylene;

$R^{12} - Z^2$ is $alkyl - NH - \overset{O}{\parallel} C -$ or $R^{12a} - \overset{O}{\parallel} C -$; and

15 R^{12a} is alkyl, fluorinated lower alkyl or
polyfluorinated lower alkyl.

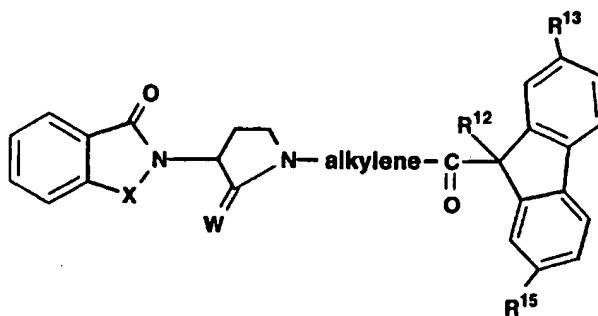
10. The compound as defined in Claim 9
wherein R^{11} is $-(CH_2)_4-$, Z^1 is a bond, and $R^{12} - Z^2$ is
 $CH_3(CH_2)_2 - \overset{O}{\parallel} C - NH -$ or $CF_3CH_2 - \overset{O}{\parallel} C - NH -$.

20 11. The compound as defined in Claim 9
having the structure



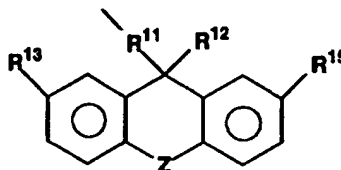
25 where R^{13} and R^{15} are independently H or F, and R^{12}
is trifluoromethylalkyl or alkyl.

12. The compound as defined in Claim 9
having the structure



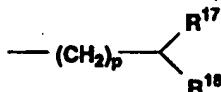
where R^{12} is alkyl, and R^{13} and R^{15} are
5 independently H or F.

13. The compound as defined in Claim 1
wherein R^1 is arylalkyl, arylalkenyl,
heteroarylalkyl, heteroarylalkenyl,



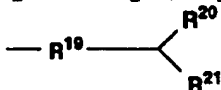
10

where R^{11} is alkylene or alkenylene; R^{12} is H,
alkyl, alkenyl, aralkyl, aralkenyl; and R^{13} is H or
F; and R^{15} is H or F; Z is O, S or a bond; or R^1 is



15 wherein $(CH_2)_p$ represents an alkylene chain or cis
alkenylene of up to 6 carbons;

R^{17} and R^{18} are each independently alkyl,
alkenyl, aryl, arylalkyl, heteroaryl, heteroaryl-
alkyl, cycloalkyl, cycloalkylalkyl; or R^1 is

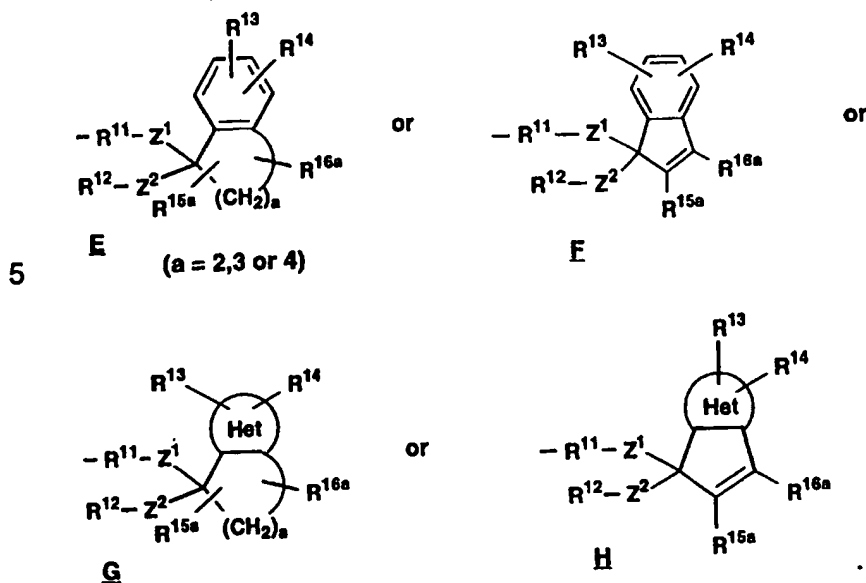


20

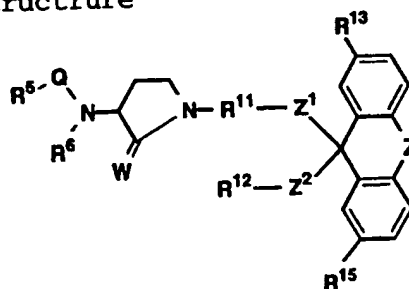
R^{19} is aryl or heteroaryl; R^{20} is aryl or
heteroaryl;

R^{21} is H, alkyl, aryl, alkylaryl, arylalkyl,
aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl,
25 heteroarylalkoxy, cycloalkyl, cycloalkylalkyl, or
cycloalkylalkoxy.

14. The compound as defined in Claim 1 wherein R¹ is an indenyl-type group of the structure



15. The compound as defined in Claim 1 having the structure



where Q is $\text{--}\overset{\text{O}}{\parallel}\text{C--}$ or $\text{--}\overset{\text{O}}{\parallel}\text{S--}$;

Z is a bond, O or S;

where R⁵ is cycloalkyl, phenyl, aryl,

15 heteroaryl, or cycloalkyl, phenyl, aryl or heteroaryl, independently substituted at the ortho position with alkyl, alkoxy, haloalkyl (optionally substituted with up to 5 halogens), trifluoromethyl, aryl, aryloxy, haloalkoxy (optionally

substituted with up to 5 halogens), arylalkyl or arylalkoxy;

R^6 is H or CH_3 ;

R^{13} and R^{15} are independently H or F;

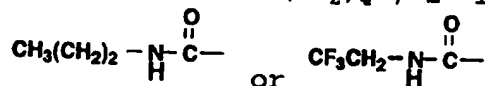
5

Z^1 is a bond;

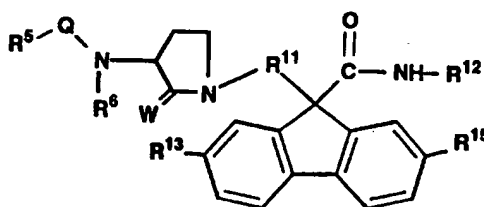
R^{11} is alkylene;

$R^{12} - Z^2$ is $\text{alkyl}-\text{NH}-\overset{\text{O}}{\parallel}{\text{C}}-$ or $\text{CF}_3\text{alkylNHC}-\overset{\text{O}}{\parallel}{\text{C}}-$,
or Z^2 is a bond and R^{12} is alkyl.

16. The compound as defined in Claim 15
10 wherein R^{11} is $-(CH_2)_4-$, Z^1 is a bond, and $R^{12}-Z^2$ is



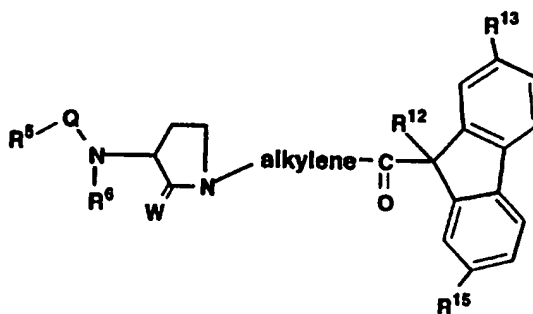
17. The compound as defined in Claim 15
having the structure



15

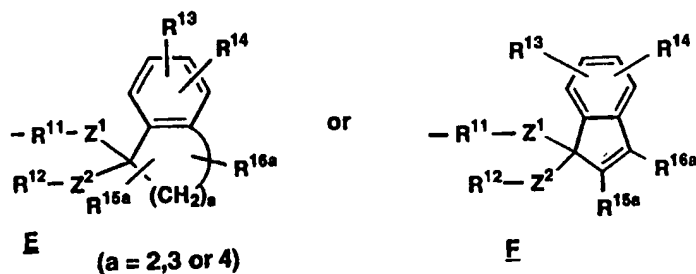
and R^{12} is trifluoromethylalkyl or alkyl.

18. The compound as defined in Claim 15
having the structure

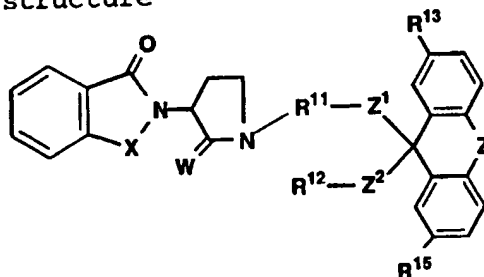


20 where R^{12} is alkyl.

19. The compound as defined in Claim 1
wherein R^1 is a group of the structure



20. The compound as defined in Claim 1 having the structure



5

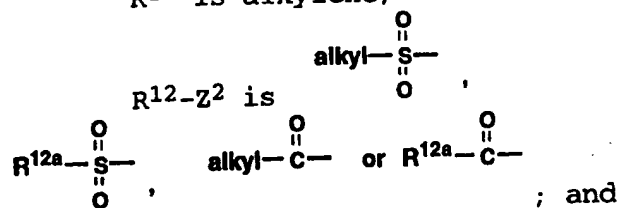
Z is O, S or a bond;

R¹³ and R¹⁵ are independently H or F;

Z¹ is a bond;

R¹¹ is alkylene;

10

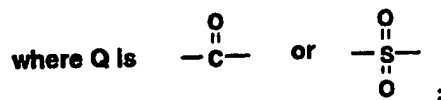
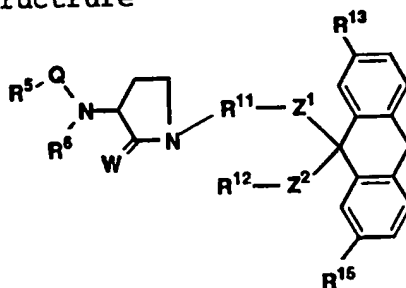


; and

R^{12a} is alkyl, fluorinated lower alkyl or polyfluorinated lower alkyl.

21. The compound as defined in Claim 1 having the structure

15



Z is a bond, O or S;

where R⁵ is cycloalkyl, phenyl, aryl, heteroaryl, or cycloalkyl, phenyl, aryl or heteroaryl, independently substituted at the ortho position with alkyl, alkoxy, haloalkyl (optionally substituted with up to 5 halogens), trifluoromethyl, aryl, aryloxy, haloalkoxy (optionally substituted with up to 5 halogens), arylalkyl or arylalkoxy;

10 R⁶ is H or CH₃;

R¹³ and R¹⁵ are independently H or F;

Z¹ is a bond;

R¹¹ is alkylene;

15 R¹² - Z² is $\text{alkyl}-\overset{\text{O}}{\underset{\text{O}}{\parallel}}{\text{S}}-$, $\text{R}^{12a}-\overset{\text{O}}{\underset{\text{O}}{\parallel}}{\text{S}}-$,
 $\text{alkyl}-\overset{\text{O}}{\parallel}{\text{C}}-$ or $\text{R}^{12a}-\overset{\text{O}}{\parallel}{\text{C}}-$

R^{12a} is alkyl, fluorinated lower alkyl or polyfluorinated lower alkyl,

or Z² is a bond and R¹² is alkyl.

22. The compound as defined in Claim 1
 20 which is

9-[4-[3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

25 9-[4-[3-(benzoylamino)-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

(R)-9-[4-[3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

30 (S)-9-[4-[3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,

(R)-N-(2,2,2-trifluoroethyl)-9-[4-[3-[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-

- yl]carbonyl]amino]-1-pyrrolidinyl]butyl]-9H-fluorene-9-carboxamide,
 (S)-N-(2,2,2-trifluoroethyl)-9-[4-[3-[[4'-(1,1,1-trifluoromethyl)[1,1'-biphenyl]-2-yl]-carbonyl]amino]-1-pyrrolidinyl]butyl]-9H-fluorene-9-carboxamide,
 5 9-[4-[2-oxo-3-[[[4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-pyrrolidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,
 10 9-[4-[3-[[2-(2-benzothiazolyl)benzoyl]-amino]-2-oxo-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,
 9-[4-[2-oxo-3-[(2-phenoxybenzoyl)amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,
 15 9-[4-[3-(benzoylamino)-2-oxo-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,
 20 9-[4-[2-oxo-3-[[2-(2-pyridinyl)benzoyl]-amino]-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, or
 9-[4-[3-[[2-(4-morpholinyl)benzoyl]amino]-2-1-pyrrolidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide,
 25 or a pharmaceutically acceptable salt thereof.

23. A method for preventing, inhibiting or treating atherosclerosis, pancreatitis or obesity
 30 in a mammalian species, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

24. A method of lowering serum lipid levels, cholesterol and/or triglycerides, or inhibiting and/or treating hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia, which
5 comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/07603

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.
US CL : Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/309, 417, 418, 419, 423, 424; 546/141; 548/472, 473, 484, 485, 486, 528, 530, 532, 533

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,416,009 A (HARTMAN et al.) 16 May 1995, columns 2-4, entire discloser.	1-24
A	US 5,362,736 A (ISHIKAWA et al.) 08 November 1994, column 1, formula I.	1-24
A	US 5,304,556 A (YAMAMOTO et al.) 19 April 1994, column 2, compound of formula (I), line 60.	1-24
A	US 4,459,414 A (FISCHER et al.) 10 July 1984, entire discloser in columns 1 and 2.	1-24
A	US 3,740,415 A (KASHIHARA et al.) 19 June 1973, columns 1 and 2.	1-24

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	* T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
* A* document defining the general state of the art which is not considered to be of particular relevance	* X	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
* E* earlier document published on or after the international filing date	* Y	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
* L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	* A*	document member of the same patent family
* O* document referring to an oral disclosure, use, exhibition or other means		
* P* document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
01 JULY 1997

Date of mailing of the international search report
24 JUL 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Authorized officer

YOGENDRA N. GUPTA

Facsimile No. (703) 305-3230

Telephone No. (703) 308-1235

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/07603

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/07603

A. CLASSIFICATION OF SUBJECT MATTER: IPC (6):

C07D 207/12, 209/12, 209/34, 217/24, 401/04; A61K 31/405, 31/47, 31/395

A. CLASSIFICATION OF SUBJECT MATTER: US CL :

514/309, 417, 418, 419, 423, 424; 546/141; 548/472, 473, 484, 485, 486, 528, 530, 532, 533

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-4, 7-14, 19, 20 and 22-24, drawn to mixed heterocyclic compounds.

Group II, claims 1, 2, 5-8, 13-19 and 21-24, drawn to pyrrolidine compounds.

The inventions listed as Groups I and II do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The compounds of inventions I and II are drawn to structurally dissimilar compounds. They are made and used independently. They are independent. If, say, invention of Group I, the mixed heterocyclic compounds, were anticipated, applicants would not acquiesce in objection of Group II compounds there over or vice-versa. They inventions of Groups I and II are distinct.